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CONTINUOUS AGGLOMERATION PROCESSES USING A TWIN SCREW EXTRUDER

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1 Introduction

1.1 Wet granulation

Wet granulation is a well-established and widely used technique in industries processing food, chemicals, detergents, fertilisers and pharmaceuticals. More than 70% of the global industry's granulations are made using wet granulation (Ennis, 1997). Wet granulation of powders refers to the process whereby aggregates with sizes ranging from about 0.1 to 2.0 mm are produced and can be defined as a process whereby particles are agglomerated into larger semi-permanent aggregates, in which the original particles can still be identified. These granules are formed by spraying a liquid binder onto the particles while they are agitated in a tumbling drum, fluid bed, high shear mixer or similar device (Ennis and Litster, 1997; Kristensen and Schaefer, 1987).

Addition of the proper amount of liquid wets the solid surfaces and generates the necessary binding forces by the formation of liquid bridges or by a combination of capillary pressure, surface tension and viscous forces, until more permanent bonds are formed during subsequent drying or sintering.

Granulation has many advantages like the improvement of flow, the reduction of segregation and dust and the enhancement of compressibility. Besides it ensures the production of products with a consistent quality.

On the other hand improper granulation causes problems such as caking, segregation and poor tableting properties in the down-stream processes. Therefore, wet granulation is considered to be one of the most critical unit operations in the manufacturing of solid dosage forms such as granules, pellets and tablets.

Granulation is a very complicated process and difficult to master due to the numerous and sometimes unknown factors that can affect the process and hence the product properties. Therefore, almost everything associated with the wet granulation process such as material properties, equipment, batch size, amount of binder solution and processing time must be controlled if one is to have a reproducible product and to ensure the production of granules with desired properties. However, in order to

elucidate the importance of these parameters granulation growth, liquid saturation, binder addition and wet granulation equipment will be discussed.

1.2 Granule growth

The growth process begins as soon as liquid is added to the agitated powder mass and may continue after the liquid addition step has been completed. The growth of granules, which occurs during liquid addition and kneading, has been divided into three stages, as shown in figure 1:

a Nucleation of particles.

b Coalescence between colliding agglomerates.

c Layering of smaller particles onto established agglomerates.

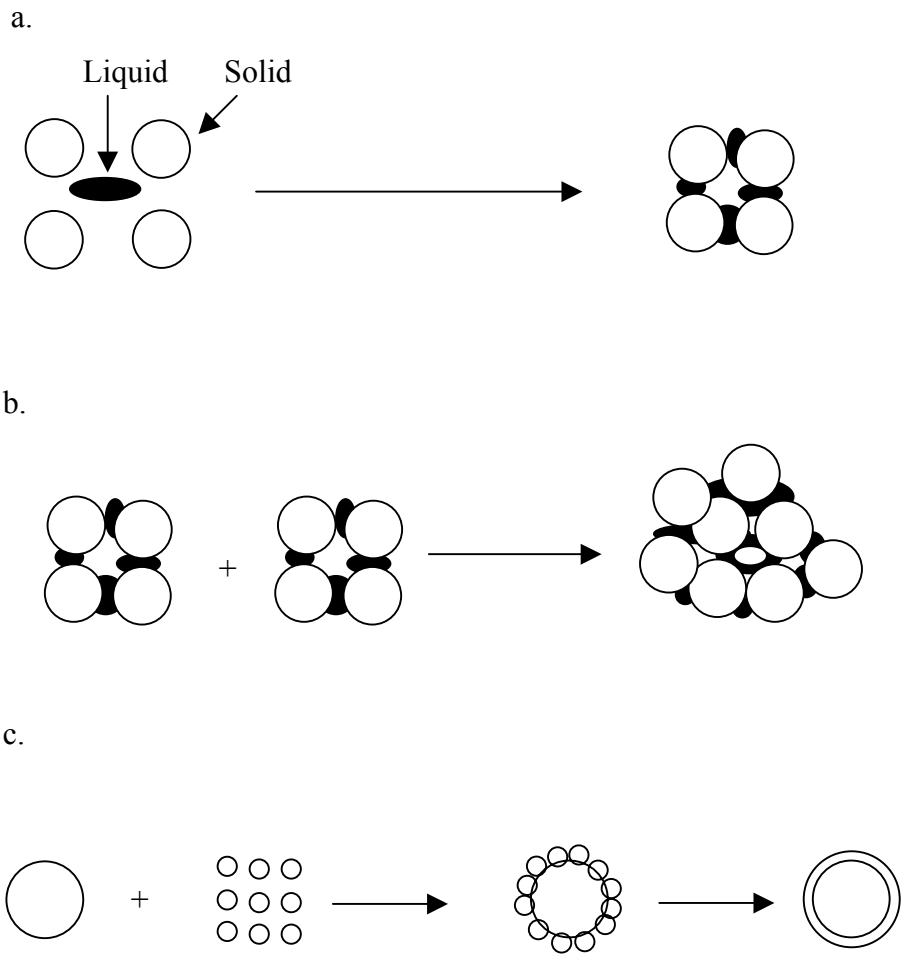

Figure 1: Mechanism of wet granulation: a. nucleation, b. coalescence, c. layering.

Whenever a powder is mixed with a liquid, the liquid wets the particle surface and the system tends to reduce its surface free energy by forming liquid bridges between the particles. If the strength of the liquid bridges is sufficient to withstand the separating forces caused by agitation, the particles stick together in the form of a loose agglomerate called nucleus.

Agglomeration of the powder may proceed by further nucleation and by coalescence or layering depending on the particle size and size distribution of the material.

The sticking of two large granules is referred to as coalescence, whereas the sticking of the fine materials onto the surface of large pre-existing granules is often termed layering. Coalescence will be the dominant growth mechanism if the agglomerates possess a high agglomerate strength (Tardos et al., 1997).

Growth by coalescence continues until a critical agglomerate size has been reached (Ennis et al., 1991). This critical size is higher when the viscosity of the binder is high and for powders with a smaller particle size. Agitation gradually consolidates the formed agglomerates by increasing their liquid pore consolidation as they collide with each other and with the surface of the granulator.

Agglomeration can only resist deformation and breakage below the critical agglomerate size, which depends on the external applied energy and the agglomerate strength (Tardos et al., 1997). If the agglomerates are too weak to resist the impact and shear forces in the mixer, agglomerate breakage will occur simultaneously with growth by coalescence (Knight et al., 1998; Eliason et al., 1998, 1999). As a result, particles and small fragments formed by breakage might participate in growth by layering as the smaller fragments are layered on the surface of surviving agglomerates (Linkson et al., 1973). At this stage the granulation process will operate in a balance between agglomerate growth and degradation.

Although a qualitative understanding of the mechanisms of granule growth and the effect of different variables on granule growth behaviour are available, it is still difficult to predict the granulation behaviour of a new formulation from only its fundamental properties. This necessitates extensive experimental studies for new materials and formulations.

1.2.1 Liquid saturation

Liquid saturation of the agglomerates during wet granulation is an essential parameter controlling granule growth. Liquid saturation (S) is the degree of intergranular voids filled with liquid phase and is controlled by the liquid content and intergranular porosity. It is determined from the intergranular porosity $\in$, particle density ρ and the moisture content H of the granules on dry basis.

$$S = \{H (1 - \in)/\in\}*\rho \qquad \text{(equation 1)}$$

It is well known that amount of the liquid required for the production of satisfactory granules depends on a large number of factors, which include powder properties, liquid characteristics and the granulation technique used. Powder properties such as particle size distribution, particle shape, solubility and ability to absorb liquid play a significant role in respect to the amount of liquid required and agglomerate growth. Particles having a mean particle size below 10 μm are usually difficult to agglomerate, because their cohesiveness yields agglomerates of high strength (Kristensen et al., 1985a; Schaefer, 1996b) having a reduced deformability. Therefore more binder liquid is required in order to render the agglomerates sufficiently deformable for agglomerate growth by coalescence. This increases the risk of overwetting and uncontrollable agglomerate growth. On the other hand, the agglomeration of large powder particles is also difficult. Breakage will often dominate and no agglomeration occurs because of low agglomerate strength (Newitt and Conway-Jones, 1958). However, a comprehensive knowledge of the properties of the materials to be granulated can help in predicting the amount of the granulation liquid required and the process conditions in order to conduct a successful wet granulation. An increase in the solubility of the solids corresponds to a decrease in the amount of liquid required (Lustig-Gustafsson et al., 1999).

Liquid characteristics include viscosity, surface tension and its ability to fill the void spaces of the powder (Hancock et al., 1994). However, if the amount of water could be predicted before granulation trials this would offer many advantages during development and scaling-up of the granulation process. In this context, Schaefer and Worts (1978) and Watano et al. (1991) reported that at steady state moisture content a

correlation exist between the particle size and the moisture content, hence a suitable moisture content for formulations could be determined.

Newitt and Conway-Jones (1958) described the different states of liquid saturation representing the stages of liquid distribution in a bed of solid particles (Fig. 2).

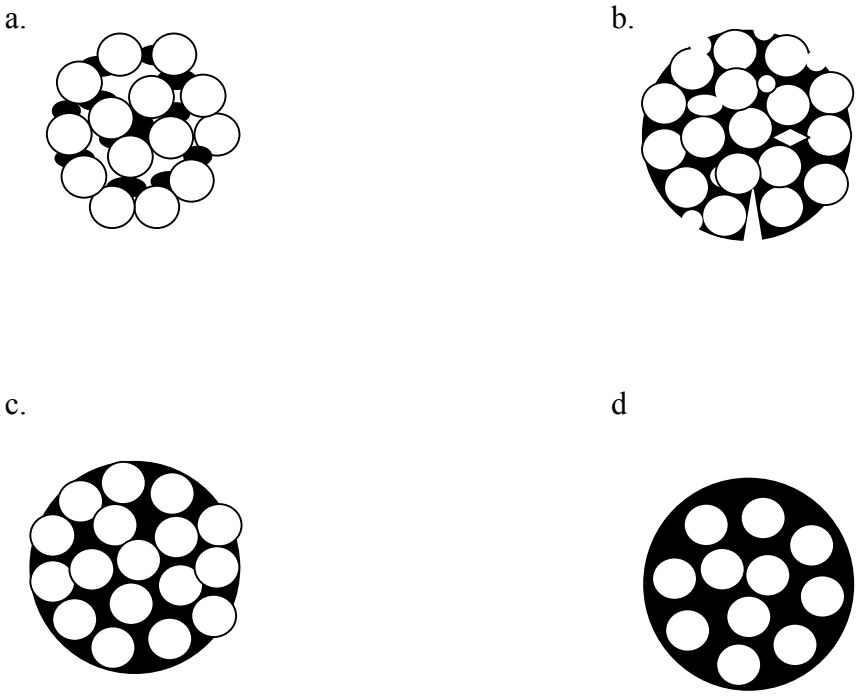

Figure 2: Different stages of liquid saturation during granulation: (a) pendular state, (b) funicular state, (c) capillary state and (d) droplet state.

In the pendular state (where the relative amount of the liquid phase in the wet agglomerates is about 25%) the individual particles create liquid bridges between them by holding the liquid at the points of contact, the contributing forces are surface tension and negative suction pressure due to the curvature of the liquid. As soon as the liquid bridges that can be created are formed, the agglomerates reach an average critical size.

By continuous addition of the granulation liquid the interparticle pore volume is filled and the wet particles reach the funicular state (the relative amount of liquid phase in wet agglomerates is 25 to 80%). When the interparticle pores are entirely filled by the liquid, the agglomerates are saturated and the mixture reaches the capillary state (the relative amount of liquid phase in the wet agglomerate is > 80%). Then the liquid will

be used to create liquid bridges between agglomerates, filling the new spaces created between agglomerates. Once these new pores are completely filled the state of liquid dispersion is reached. In this stage the liquid surrounds the solid particles.

1.2.2 Incorporation of binders

In wet granulation the role of binders is to promote size enlargement. The presence of a binder will determine the physical properties of granules as well as their consolidation and compaction behaviour. Consolidation of moist agglomerates is a basic mechanism involved in granule growth. This effect is largely determined by the type of binder (Krycer et al., 1983), the binder concentration and the method of incorporation (Rue et al., 1980; Reading and Spring, 1984). The growth of agglomerates is affected by binder viscosity as the agglomerate formation and growth depend on the distribution of the liquid binder, which is facilitated by a low binder viscosity. The subsequent growth by coalescence is promoted by a high binder viscosity (Ennis et al., 1991; Schaefer and Mathiesen, 1996 b), but it could result in uncontrolled agglomerate growth. A high viscosity could also result in an inhomogeneous binder distribution and hence in weak granules due to insufficient bonding. On the other hand a high binder viscosity can act as a lubricant, reducing the power consumption during granulation. Therefore, the selection of a suitable binder and the optimisation of its concentration are important in order to achieve a successful granulation.

The minimum binder viscosity required to form granules increases with the particle size of the solid material (Keningley et al., 1997), as a lower binder viscosity and a large particle size will decrease the agglomerate strength (Keningley et al., 1997) and produce more fines (Ormos et al., 1973; Ragnarson and Sjoren, 1982).

1.3 Effect of granule quality on the tablet properties

As granulation is mostly intended for the preparation of tablets the compaction process as well as the properties of tablets depend on granule characteristics such as porosity, friability, pore size distribution, size distribution and density.

Porosity controls the strength of the granules. Highly porous granules are weak and friable and could break during handling generating dust, which is undesirable in most

cases. On the other hand it is desirable to produce porous granules, since it will facilitate compaction as the fragmentation of granules during compression is related to granule porosity before compression (Wikberg and Alderborn, 1991). Granules with higher porosity have a higher fragmentation propensity and result in stronger tablets. Relatively dense and compact granules require a lot of mechanical force in order to be compressed into tablets. A low bulk density of the granules resulted in an increase in the compactability of the granule bed during compression (Zuurman et al., 1994).

Strong granules (i.e. low friability) are advantageous for subsequent steps in the production process (such as final mixing and transport) because friable granules have a detrimental effect on flow and can cause demixing. Therefore, a granule friability below 50% (Inghelbrecht and Remon, 1998) is important for handling and subsequent processing (mixing and feeding into the hopper) during tablet production.

Granule size can also affect the compaction properties of the granules. Stronger tablets were obtained with a decreasing size of the granules (Wells and Walker, 1983; Wikberg and Alderborn, 1990). Because coarse granules possess a smaller surface area less lubricant will be required to obtain smooth compaction. On the contrary smaller granules could result in sticking problems during compression due to insufficient lubrication. In addition, too many fines in the granules can result in tablet capping.

The granule properties not only affect tablet strength, but also the disintegration and dissolution, an increase of granule size and granule density could result in a slower tablet dissolution.

1.4 Common types of wet granulation techniques

It is known that granule properties are not only determined by the formulation variables (amount of granulation liquid, type and concentration of the binder), but also by the process parameters during granulation and the granulation technique.

Wet granulation offers a wide range of techniques for granule formation, from the production of porous granules to the production of dense agglomerates depending on the type of granulator used. Several types of wet granulators are available, each granulation process resulting in different granule characteristics. The wet granulators can be classified as following:

- Low shear granulators (planetary mixer granulators, cone mixer granulators and Z- blade mixer granulators).

- High shear granulators (horizontal mixer/granulator, vertical mixer/granulator).

- Fluid bed granulators (top spray fluid bed, rotor fluid bed).

In the pharmaceutical industry the two most frequently used wet granulation techniques are high shear granulation and fluid bed granulation.

1.4.1 High shear granulation

High shear granulation is characterised by the fact that mixing of the powder and granulation takes place in the same apparatus. This type of granulator is equipped with an impeller rotating at a moderately high speed (100 to 500 rpm) and a chopper rotating at higher speed. Mixing, agglomeration and densification of wetted materials are achieved through shearing and compaction forces exerted by the main impeller. The binding liquid can be poured, pumped or spray atomised onto the powder. High shear granulation has some major advantages such as the fact that a broad range of powders (in both particle size and bulk density) can be processed, a significant increase in the bulk density of granules over that of the starting materials and a short process time for both mixing and granulation. The main disadvantages of high shear granulation are: the significant increase in the bulk density of the granules, an uncontrolled growth of the granules and the different handling steps between the unit operations. However, in recent years, high shear granulators have been introduced that allow wet granules to be dried inside the granulation bowl by either gas stripping or microwave drying.

1.4.2 Fluid bed granulation

Fluid beds are commonly used granulators in pharmaceutical industry, which produce porous granules. It was first described by Wurster in 1959. The major advantages of fluid bed granulation are that granule growth can be controlled, a low batch-to-batch variation and no product handling is required since mixing, granulation and drying

can take place in the same machine. In addition it is also used for coating and pelletisation.

The principle of fluid bed granulation is drawing air through a conical shaped container by a ventilator, which is set to move the particles up in the central part of the expansion chamber and down again at the walls. The fluidising air is heated to a temperature typically ranging from 40 to 80°C. The binding solution is added by spraying.

Due to the lack of shear forces in the fluid bed, many powders have to be delumped by sieving before loading into the machine.

Granulation in fluid bed takes place in a well controlled manner and results in granules with a moderate bulk density, which are suitable for compression into tablets. However, the process is not suitable for granulation of coarse materials, cohesive materials and voluminous powders.

Fluid bed granulation is described as a complex process which is influenced by several process parameters (Rambali et al., 2003). Acceptable results are not always obtained (Rambali et al., 2001) because the granule size depends on fundamental properties such as droplet size of the binder solution sprayed onto the powder and powder bed moisture content (Rambali et al., 2001; Schaefer and Worts, 1978; Watano et al., 1996 a, b, c), but it remains a suitable process to prepare granules for tabletting, because the lack of any shear forces during granulation results in low strength, porous granules (Sunada et al., 1998).

1.5 Extrusion

1.5.1 Introduction

Extrusion is another possible way of producing granules. It involves a process of forcing a material through an orifice by means of pressure. Materials can be extruded in the solid state using a liquid which acts as a plasticiser or in the molten state using a heated extrusion barrel (melt extrusion). The extruded product is referred to as extrudate (Morton-Jones, 1989; Rauwendal, 1994).

Rauwendal (1994) classified extruders, depending on their mode of operation, into two main groups: continuous and discontinuous (batch type) extruders as shown in figure 3. Discontinuous extruders operate in a cyclic way and have a reciprocating

member to transport the material, whereas continuous extruders are capable of developing a steady continuous flow of materials utilising a rotating member to transport the materials. The continuous extruders can further be subdivided into disk extruders, drum extruders and screw extruders. The screw extruders are also classified, based on the number of screws incorporated, into single, twin and multi-screw extruders. Twin screw extruders are further classified into co-rotating and counter-rotating types.

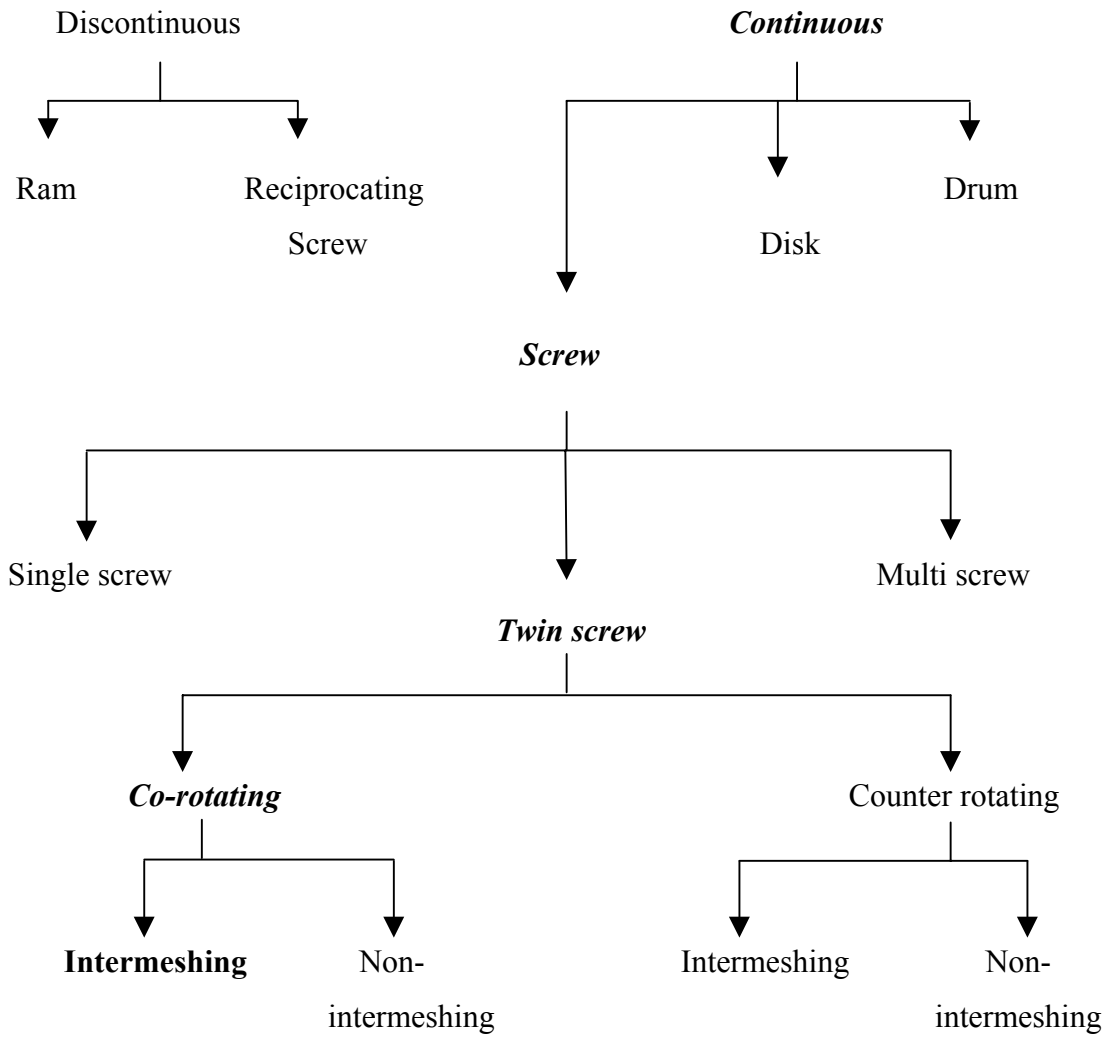

Figure 3: Classification of the extruders

Although the extrusion technique is widely used in the pharmaceutical industry for the production of pellets, few research work has been done in order to use extrusion for the production of granules (extrusion/granulation) (Gamlen and Eardley, 1986;

Lindberg et al., 1987; Lindberg, 1988a, b). Although granulation using single screw extruders has been reported (Goodheart et al., 1973), the majority of extrusion granulation studies were carried out using twin screw extruders. Gamlen and Eardley (1986) reported on the production of paracetamol extrudates using twin screw extrusion and stated that the short time from wetting to extrusion was the most significant advantage of this process. Lindberg et al. (1988a) found that screw speed and powder feed rate were the significant factors influencing the mean residence time. Kleinebudde and Lindner (1993) stated that the water content of extrudate has an important influence on the extrusion parameters. As a co-rotating twin screw extruder is used in this research project it will be further described.

1.5.2 Twin screw extruder

The extruder used during this study is an intermeshing co-rotating twin screw extruder type MP19 TC-25 (APV Baker, Newcastle-under-Lyme, UK) with a length to diameter ratio of 25/1. As illustrated in figure 4 the extruder is composed of a barrel, a control panel and a driving unit. It is also equipped with a Brabender twin screw powder feeder, a Technodrives DC motor, a Tricool cooling system and a peristaltic pump (for introducing the granulation liquid).

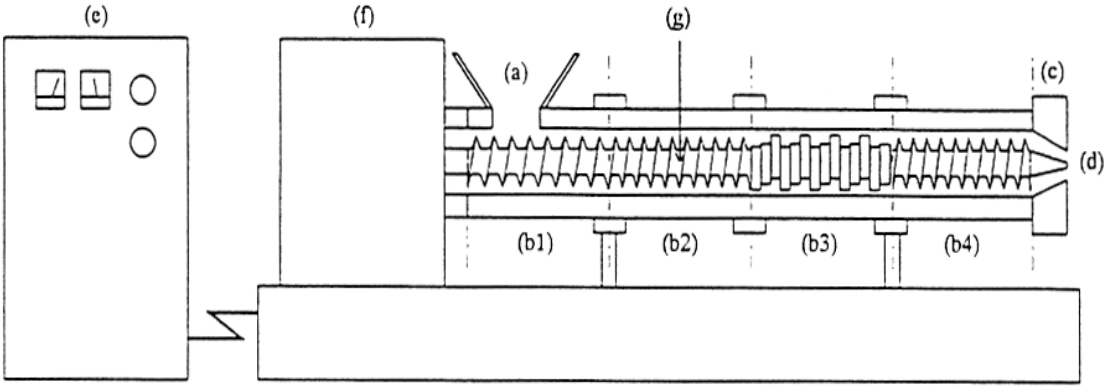

Figure 4: Schematic diagram of a twin screw extruder with a) feeding hopper, b) barrel, c) die block, d) die, e) control panel, f) driving unit, g) screws.

The control panel is used for setting the screw speed, the barrel temperature and the powder feed rate. Processing parameters such as die pressure, actual barrel

temperature and power consumption are recorded during the process and shown on the control panel. The extruder barrel is divided into five zones of which the temperature can be set individually.

The screws used in this study had a standard design composed of seven zones as shown in figure 5. These zones are: a conveying zone, a transition zone, a first mixing zone, a second conveying zone, a second mixing zone, a third conveying zone, a feed zone towards the die. The function of these zones is described below:

Zone 1: conveying zone

This zone is composed of conveying elements and functions to receive the powder and transport it forward. It also mixes and smoothens out any instability in the powder feed rate.

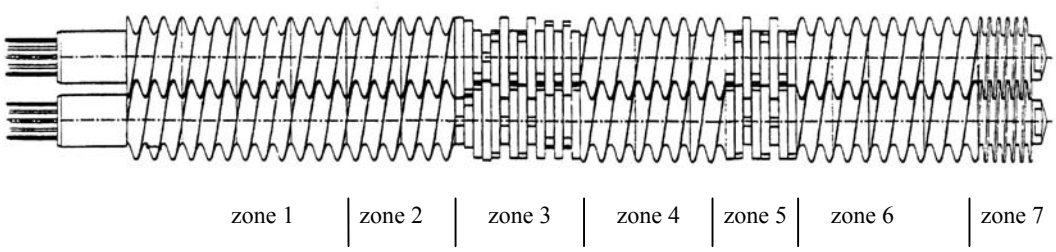

Figure 5: The design of the co-rotating twin screw (MP 19 TC-25).

Zone 2: transition zone

This zone is composed of conveying elements. The granulation liquid is added at this zone. It also mixes the powder with the granulation liquid and conveys the wet mass to the next zone.

Zone 3: first mixing zone or agglomeration zone

This zone is composed of 10 mixing paddles (3 mm thick) fixed perpendicularly to the screw axis. These paddles compress the wet mass and enhance mixing, agglomeration and densification. Another function of this zone is the homogenisation of powder and binding liquid.

Zone 4: second conveying zone

This zone is composed of conveying elements. It mixes and breaks down the agglomerates formed in the first agglomeration zone and conveys the agglomerated material to the next zone.

Zone 5: second mixing zone or agglomeration zone

This zone is composed of 6 mixing paddles. At this zone further agglomeration and densification of the material takes place.

Zone 6: third conveying zone

This zone is composed of conveying elements. It breaks down the agglomerates formed in the second agglomeration zone and conveys the agglomerated material to the next zone.

Zone 7: feed zone towards the die

This zone is composed of densification element. Because of the structure of this zone accumulation of agglomerates occurs, resulting in an increased pressure.

1.5.3 Extrusion/granulation parameters

It is known that agglomeration is caused by the complex interaction of several processing and formulation variables. The knowledge of the influence of each variable is essential for controlling the process as well as for obtaining the desired granule properties. During continuous granulation controlling those parameters is even more critical since the granulation process is run over a long period and a constant granule quality is required at all times.

During extrusion/granulation using a twin screw extruder, the following process parameters and formulation variables influence the granulation process and the resulting granules:

- Screw speed
- Total feed rate (powder and liquid feed rate)
- Screw design
- Barrel temperature

- Water concentration
- Binder type, concentration and way of addition

1.6 Continuous wet granulation

Although in pharmaceutical manufacturing several individual operations are carried out in a continuous way (e. g. milling, tabletting and packaging) the production of granules is still, to a large extent, a batch-wise process. This production method provides an advantage towards quality assurance as the batch can be accepted or rejected. However, the increasing demand of pharmaceutical solid dosage forms necessitates the production of larger volumes of granules, requiring larger equipment. Hence it demands more capital investment, companies have to dedicate more resources to it (personnel and space) and it complicates the scale-up process (Leuenberger, 2001). Therefore, continuous granulation becomes an interesting process to the pharmaceutical industry because the same equipment can process smaller as well as large quantities by just extending the process time, thus eliminating any scale-up issues.

Continuous granulation involves the use of a suitable device to continuously mix, wet mass and discharge the ingredients of a pharmaceutical formulation to produce granules suitable for drying and subsequent handling (Lindberg, 1988b). In the recent years there is a growing interest in the pharmaceutical industry for continuous wet granulation as an alternative approach for batch-wise processing. The rationale behind this interest are the advantages offered by continuous granulation (Lindberg, 1988b; Leuenberger, 2001):

1 High production capacity
2 Reduction of cost and labour
3 Saving on space and time
4 Ease of automation
5 Avoiding scale up problems
6 Flexibility of batch size
7 Minimal wastage and less product at risk

However, some disadvantages of continuous granulation were also reported (Lindberg, 1988b; Leuenberger, 2001):

1. Limited applicability of continuous granulation within the pharmaceutical industry as the pharmaceutical plant typically manufactures numerous products at a small volume, whereas continuous production is best suited for production of a single high-volume product
2. The process is not suitable to process substances sensitive to heat or moisture
3. Moisture content (hence quality) of the granules depends on the accuracy of the powder and liquid dosing system
4. The absence of a batch size, even though batches during continuous processing have been defined by the amount of material produced within a working shift or within a period of 24 hours
5. Formulations containing several low-dosed components require a pre-blending stage
6. Viscous granulation solutions are difficult to pump
7. Powders with poor flow properties can not be dispensed accurately by the feeder
8. After starting the process it takes some time to achieve equilibration conditions

As all conventional machines for wet granulation (high shear and fluidised bed granulation) can only be operated in a batch-wise manner, several attempts have been made to develop continuous wet granulation techniques.

Bonde (1998) classified the existing continuous granulators into two groups: continuous fluid bed granulators and continuous mechanical granulators. Although roller compaction can be considered as a continuous mechanical dry granulation process this technique will not be discussed as the topic of this project is wet granulation.

Research was conducted on the fluid bed granulator in order to run it in a continuous manner. A continuously operating single cell fluid bed granulator was described by Hajdu et al. (1984), which simultaneously mixed, agglomerated and dried. However, the differences in process conditions required for each granulation experiment make it complicated and difficult to achieve. A multi-cell fluid bed granulator was developed to overcome the problems associated with the single cell fluid bed granulator. It comprises of a horizontal processing chamber divided into a number of segments by

means of doors which can be opened or closed according to the current stage of the granulation process. Unfortunately, these machines were not accepted in the pharmaceutical industry due to their complexity and the poor co-ordination between mixing, agglomeration and drying. In the past years some, more acceptable, continuous fluid bed techniques (Contipharm from Niro/Aeromatic-fielder and Continuous Fluid Bed Granulator from Glatt) were developed to avoid the problems associated with the above mentioned multi-cell fluid bed granulator. Research work conducted on these machines showed a random mixing and transport of materials within the product chamber (Gotthardt et al., 1999).

The quasi-continuous production which combines a high shear granulator and the multicell fluid bed dryer is another attempt to achieve a continuous wet granulation (Leuenberger, 2001). This technique is based on semi-continuous production of small batches (mini-batches) per unit time, as a consequence the amount of material processed could be varied. This technique has the advantage of avoiding scale-up, which can be conducted by extending the production time. The batch size is no longer determined by the machine size, but by the working time or the number of mini-batches produced. Granulation carried out using this technique showed a good reproducibility between the mini-batches produced in terms of granule and tablet properties, however the process appeared slightly complicated as an exact co-ordination between the granulator and drying units is required. Nevertheless, this machine found some acceptance in the pharmaceutical industry (Leuenberger, 2001).

Within the continuous mechanical granulators two techniques are discussed: turbine mixer granulation and extrusion/granulation. The turbine mixer granulator was described by Bonde (1998) and Lindberg (1988a). It contains a high-speed turbine used to disperse the powder and break up the granulation liquid into small droplets, forming agglomerates during the very short residence time in the granulation chamber. This granulator is characterised by a very high production capacity.

Research work on the use of extrusion for continuous wet granulation of pharmaceuticals is very sparse. Gamlen and Eardley (1986) used a Baker-Perkins MP 50 twin screw extruder for the extrusion of a paracetamol formulation at a high drug load. Although these formulations were satisfactorily granulated during the short residence time in the extrusion barrel, this process revealed serious problems like die blocking and material sticking. Lindberg et al. (1987) and Lindberg (1988b) evaluated continuous wet granulation of an effervescent mixture using the Baker-Perkins MPF

50D twin screw extruder and reported similar problems as Gamlen and Eardley (1986). However, no data describing the properties of the granules produced by extrusion/granulation have been reported.

Schroeder and Steffens (2002) described a continuous wet granulation system using a modified planetary roller extruder in combination with gas injection to adjust the porosity and to improve the tabletting properties.

Recently Ghebre-Sellassie et al. (2002) presented a twin screw granulator/chopper as a continuous wet granulator/dryer system. This system is composed of a twin screw granulator/chopper to agglomerate the powder, at the outlet of the extruder a belt conveyer continuously transports the wet granules to a microwave dryer and finally the granules to a size reduction mill.

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2 Objectives

In recent years there is a clear trend within the pharmaceutical industry towards increasing the production scale, fast running processes and increasing GMP and validation requirements. As granulation is an essential unit-operation during the manufacturing of pharmaceuticals, these factors have stressed the need to develop a granulation process which has as few steps as possible and is able to work continuously without the need for expensive and time consuming scale-up trials. As granulation using an extruder offers these possibilities, the overall aim was to develop a wet granulation process using extrusion that complies with the needs of the pharmaceutical industry to reduce development time and costs as well as to minimize the scaling-up efforts.

The first part evaluates an extrusion/granulation process using twin screw extrusion in combination with a wet sizing step. It includes the evaluation and optimisation of process parameters and formulation variables (placebo formulations containing lactose as well as formulations containing high drug dose) by assessing the process efficacy based on the granule and tablet properties obtained.

The second part of the study deals with the development of a fully continuous granulation technique using a modified twin screw extruder and also evaluates the influence of processing and formulation variables on granule and tablet quality (for placebo and drug formulations). An essential step is also to determine if the process can be run continuously and to quantify the capacity of this technique.

The third part of the study assesses the feasibility of performing a continuous single step granulation/tabletting process using cold extrusion and evaluates the parameters influencing tablet quality. This part also describes the bonding mechanism between particles in tablets prepared by this technique.

The final part describes the influence of storage conditions (relative humidity and temperature) on the stability of tablets produced by the different techniques developed in the previous chapters.

3 Continuous twin screw extrusion for the wet granulation of lactose

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3.1 Introduction

In the field of solid dosage forms wet granulation is still frequently used during tablet production. Over the past decades, several batch-wise wet granulation techniques, such as high shear and fluid bed granulation, have been developed and extensively studied. As continuous processing offers significant advantages over batch production (automation and a reduction of batch-to-batch variation, labor cost and processing time), several types of equipment allowing continuous wet granulation have been developed, the main types being continuously operating mixer granulators and fluid bed granulators (Bonde, 1998). In addition some reports indicated the potential of twin screw extrusion as a continuous wet granulation technique. Gamlen and Eardley (1986) studied the influence of formulation parameters on the quality of paracetamol extrudates. These authors stated that, despite the high incidence of extrudate surface defects, the extrusion technique was suitable for the granulation of paracetamol. Other researchers (Lindberg et al., 1987, 1988; Lindberg, 1988) showed that wet granulation via extrusion yielded granules with desired properties and that those properties were influenced by formulation and process variables. Kleinebudde and Lindner (1993) studied the twin-screw extrusion/granulation process using lactose/microcrystalline cellulose, but did not evaluate granule characteristics. The purpose of the present work was to study the influence of the formulation variables and process parameters on the production of α-lactose monohydrate granules using continuous twin screw extrusion and to compare this technique with high shear granulation, a well established wet granulation technique in the pharmaceutical industry.

3.2 Materials

α-Lactose monohydrate 200M was obtained from DMV (Veghel, The Netherlands) and polyvinylpyrrolidone (PVP, Kollidon® K30) was received from BASF (Ludwigshafen, Germany).

3.3 Preparation of extrudates and granules

The extrusion was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length-to-diameter ratio of 25/1 and equipped with a standard screw profile with two mixing sections (Fig. 1). The die block (2.6 cm thick) was directly mounted at the outlet of the extruder barrel. It is designed to fit the screw ends and then the aperture gradually changes into an oval shape of 2.2 by 1.0 cm (Fig. 2). No additional screen was attached to the die block because this screen would block since low water concentrations were used during granulation.

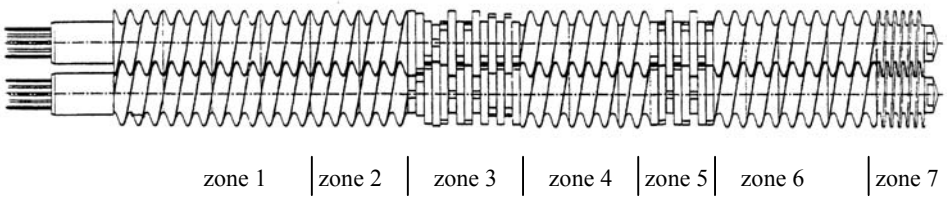


Figure 1: Co-rotating standard screw profile: feeding zone (1), transition zone (2), mixing zone (3), transport zone (4), mixing zone (5), transport zone (6) and feed zone towards the die (7).

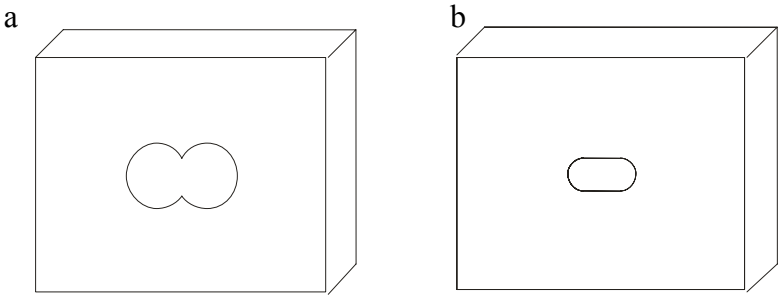


Figure 2a: Inside of the die block mounted to the extruder barrel with aperture shape to fit the screws ends.

b: Outside of the die block with oval die.

During extrusion the powder volume in the feed hopper was maintained at a constant level (85 – 100% of the total feeder capacity). Extrudates were prepared via wet and dry binder addition. The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the extruder barrel by means of a peristaltic pump (Watson Marlow, Cornwall, UK). Powder and granulation liquid feed rates were determined prior to each experiment by repeatedly weighing the powder and the liquid amount delivered over a period of 5 min. In case of dry binder addition, PVP and α-lactose monohydrate were previously blended for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK).

The barrel temperature of the extruder was set at 25°C. Extrudates were collected 10 min after the process was started in order to allow the system to equilibrate. Immediately after extrusion the extrudates (400 g) were wet sized using a 1 mm oscillating sieve (Frewitt, Fribourg, Switzerland), operated at a minimal distance between rotor and sieve. The granules were oven-dried at 25°C for 20 h, sieved through a 1400 μm sieve and evaluated for yield, granule friability, compressibility and porosity.

Based on preliminary experiments using pure α-lactose monohydrate and water (as a granulation liquid) a set of reference conditions for the extrusion process was selected: a screw speed of 250 rpm, a total input rate of 5.6 $kg.h^{-1}$ and a water concentration during extrusion of 7.5% (w/w).

These settings were used to evaluate the between day reproducibility (n=6) of the extrusion process of a formulation without PVP as well as of a mixture formulated with 2.5% PVP (wet addition). To evaluate the dissolution properties, hydrochlorothiazide (10%) (Ludeco, Brussels, Belgium) was added as a model drug to the formulation with and without 2.5% PVP (wet addition) and prepared at reference conditions. All water concentrations were based on the wet extruded mass, while PVP and hydrochlorothiazide concentrations were based on dry weight.

Fig. 3 shows an overview of the experiments performed to examine the influence of water concentration, PVP concentration and method of PVP addition (Fig. 3a) and to evaluate the influence of screw speed and total input rate (the total amount of powder and the granulation liquid fed during one hour) (Fig. 3b).

During high shear granulation, α-lactose monohydrate at a load of 0.16 $kg.l^{-1}$ was granulated without and with 2.5% PVP (wet addition) in a Gral 10 (Machines

Collette, Wommelgem, Belgium). Granulation was performed at different water concentrations (7.5, 10.0 and 12.5%) and impeller speeds (400, 500 and 600 rpm), while the chopper speed was kept constant at 3000 rpm. After a 2 min mixing period of the powder, the required amount of granulation liquid (water or an aqueous PVP solution) was continuously added over a period of 10 min using a peristaltic pump (Watson Marlow, Cornwall, UK). Wet massing was continued for 2 min following complete liquid addition. Preliminary studies on the high shear granulation showed no differences in the granule properties between granules wet sieved using an oscillating sieve and those sieved after drying. The granules prepared by high shear granulation were dried, sieved through 1400 µm sieve to remove any lumps and evaluated as described for those prepared using extrusion.

3.3.1 Compression of tablets

The granules (250-710 µm) were blended with 0.5% (w/w) magnesium stearate (<90 µm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland) for 1 min. Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN per tablet.

3.3.2 Granule evaluation

3.3.2.1 Particle size analysis

The particle size distribution of the granules ($F_{< 1400\mu m}$) was determined using laser diffraction (Master Sizer, Malvern, UK) after suspending the particles in air. The volume diameter (d_v) was used to calculate the following fractions $F_{< 250\ \mu m}$, $F_{250 - 1000\ \mu m}$ and $F_{>1000\ \mu m}$. The analysis was performed at minimal air pressure (0.4 bar) to avoid disagglomeration and/or disintegration of the granules during the test.

The surface of the granules was evaluated by scanning electron microscopy (SEM) (JSM 5600 LV scanning electron microscope, JEOL Europe, Zaventem, Belgium).

3.3.2.2 Granule porosity

The granule porosity was determined by the Autopore III mercury porosimeter (Micromeritics, Norcross, GA, USA).

3.3.2.3 Yield

The yield of the granulation process was calculated as $F_{<1400\mu m}(\%)*F_{250\text{-}1000\mu m}(\%)/ 100$ where $F_{<1400\mu m}$ is the fraction of dried granules smaller than 1400 µm and $F_{250\text{-}1000\mu m}$ is the granule fraction between 250 –1000 µm as determined during particle size analysis.

3.3.2.4 Friability

The granule friability was determined in a friabilator (PTF E Pharma Test, Hainburg, Germany), at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of granules ($F_{250\text{-}1000\ \mu m}$) together with 200 glass beads (mean diameter 4 mm) to falling shocks. Afterwards the glass beads were removed and the weight of the granules retained on a 250 µm sieve (F_{wt}) was determined after vibrating for 5 min (Retsch VE 1000, Germany) at an amplitude of 2 mm. The friability was calculated as $((I_{wt} - F_{wt})/I_{wt}) *100$.

3.3.2.5 Bulk and tapped density

The bulk volume (V_0) of 50 g granules ($F_{250\text{-}1000\ \mu m}$) was recorded in a 100 ml measuring cylinder as well as the volume after 1500 taps (V_{1500}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Bulk and tapped densities were calculated as 50 g / V_o and 50 g / $V_{1500,}$ respectively. The compressibility index (C%) was calculated from the bulk and tapped density using the following equation

$$C\% = \{(\rho_f - \rho_i) / \rho_f \} *100$$

where ρ_i is the bulk density and ρ_f is the tapped density

3.3.3 Tablet evaluation

Immediately after production tablets were stored at 25°C and 60% RH for 24 h prior to evaluation.

3.3.3.1 Tablet friability

The tablet friability was determined using a friabilator (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

3.3.3.2 Tablet tensile strength

The hardness, thickness and diameter of the tablets (n=6) was determined (PTB 311 Pharma Test, Hainburg, Germany) after a 24 h storage period at 25°C and 60% RH. The tablet tensile strength T was calculated using the equation described by Fell and Newton (1968)

$$T = 2F/\pi.d.t$$

where F, d and t denote the the diametral crushing force, the tablet diameter and the tablet thickness, respectively.

3.3.3.3 Disintegration time

The disintegration time was determined (n=6) using the apparatus described in Eur. Ph. III (PTZ-E Pharma-Test, Hainburg, Germany). Tests were performed in distilled water at 37°C using disks.

3.3.3.4 Dissolution test

Dissolution tests were performed on hydrochlorothiazide tablets in 900 ml HCl (0.1N) using the paddle method. The dissolution medium was maintained at 37 ± 0.5°C, while the rotation speed was set at 100 rpm (USP XXIII). Samples (5 ml) were withdrawn after 5, 10, 15, 20, 25, 30, 45 and 60 min and concentrations were spectrophotometrically determined at 272 nm (Beckman DU – 65, Fullerton, CA, USA).

3.4 Statistical analysis

Statistical analysis was carried out using the software package SPSS version 10.0. First the data were tested for normal distribution with a Kolmogorov-Smirnov test and the homogeneity of the variances with a Levene's test.

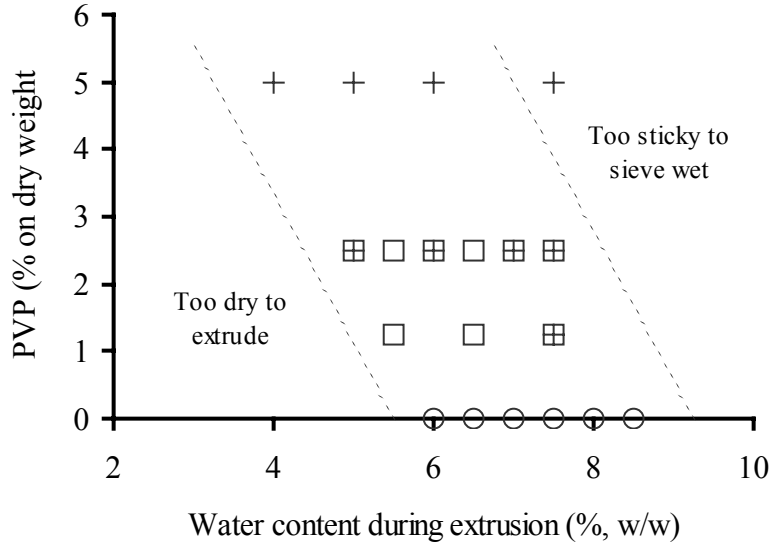
The influence of a studied parameter on the granule and tablet properties was determined using one-way ANOVA ($p<0.05$). To further compare the effects of different parameters a multiple comparison among pairs of means was performed using a Scheffe test with $p<0.05$ as a significance level. The influence of PVP concentration and addition method was evaluated only within the optimal range of water concentration. Properties of granules and tablets prepared by continuous twin screw extrusion were compared with those obtained by high shear at the respective

optimal water concentrations. Tablet friability and granule yield results could not be analyzed as only one measurement was performed per factor level.

3.5 Results and discussion

Table 1 reviews the data on the between day reproducibility of twin screw extrusion for the granulation of α-lactose monohydrate. The data indicated that the extrusion process can be considered reproducible in relation to all granule and tablet properties.
The performance of the twin screw extrusion as a granulation process at the different formulation and process parameters is visualized in Fig. 3 a and b, respectively, and shows that the extrusion/granulation process was only possible within a specific range of these parameters. The formulation parameters clearly influenced the yield (Fig. 4), whereas varying the process parameters did not (data not shown). A minimum water concentration of 6% was required for the extrusion of formulations without PVP, as the frictional forces during extrusion were too high below this water concentration. The extrudates produced without PVP at a water concentration between 6 and 7.5% could be smoothly wet sieved and resulted in a yield of ± 60%. However, a further increase of the water concentration during extrusion to 8.5% dramatically decreased the yield to 39%. This low yield is due to sticking of the material to the sieve during wet sieving as the fraction above 1400 µm was always zero and the fraction below 250 µm remained nearly constant and varied between 16 and 25%.
With respect to the yield the optimal water concentration during extrusion of pure α-lactose monohydrate ranges between 6 and 7.5%. On the other hand, the yield obtained from high shear granulation of α-lactose monohydrate without PVP never exceeded 20%, even at water concentrations above those used during extrusion (Fig. 5) (only the data obtained at 500 rpm are shown, since at this impeller speed the best results were obtained). This low yield obtained for high shear granulation is due to the improper agglomeration ($F_{< 250\ \mu m}$ 31%) (Fig. 5) combined with the high amount of lumps ($F_{> 1400\ \mu m}$ 48%) at low water concentration (7.5%) and to the high amount of lumps ($F_{> 1000\ \mu m}$ 56%) at high water concentration (12.5%). When comparing both techniques for the granulation of α-lactose monohydrate it is clear that twin screw extrusion provides an interesting alternative for conventional high shear granulation,

a



b

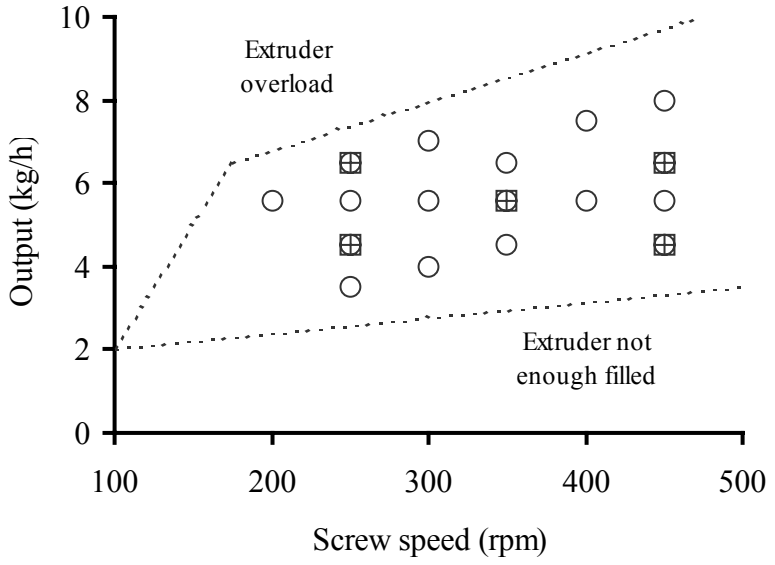


Figure 3: Overview of the experiments performed to evaluate (a) the influence of water concentration during extrusion and PVP-concentration (screw speed: 250 rpm; total input rate 5.6 $kg.h^{-1}$) and (b) the influence of screw speed and total input rate (water concentration during extrusion: 7.5%, w/w) on the properties of α-lactose monohydrate granules. Method of binder addition: (○) without PVP; (□) wet addition of PVP; (+) dry addition of PVP.

Table 1: Between day reproducibility of the wet granulation process of α-lactose monohydrate via extrusion. Granules were produced (n=6) at reference conditions without and with 2.5% PVP (wet addition) (water concentration during extrusion: 7.5% (w/w); screw speed: 250 rpm; total input rate: 5.6 $kg.h^{-1}$). Tablets were compressed at 10 kN using the 250 – 710 µm granule fraction.

	Granule properties						Tablet properties		
	Friability	**Yield**	**Particle size distribution (%)**			**Compressibility**	**Tensile strength**	**Friability**	**Disintegration**
	(%)	***(%)***	***< 250 µm***	***250-1000 µm***	***> 1000 µm***	***(%)***	***(Mpa)***	***(%)***	***(s)***
Without PVP									
	16	66	18	69	13	12.8	0.53	2.11	129
	12	63	20	67	13	9.0	0.55	1.82	149
	8	62	20	65	15	13.0	0.54	1.82	148
	24	51	38	54	9	13.5	0.48	2.12	106
	20	57	32	59	9	9.1	0.44	1.76	88
	24	58	30	64	6	8.9	0.50	2.02	120
Avg.	17	60	26	63	11	11.1	0.50	1.94	123
St. Dev.	6	5	8	5	3	2.2	0.04	0.16	24
With PVP									
	14	41	12	74	13	12.4	0.82	0.51	603
	20	40	19	72	9	14.2	0.82	0.72	571
	15	47	11	79	10	12.4	0.73	0.63	609
	22	41	18	69	14	12.4	0.85	0.71	563
	21	42	17	72	11	13.4	0.72	0.71	647
	25	37	13	73	14	12.6	0.79	0.79	694
Avg.	20	41	15	73	12	12.7	0.79	0.67	615
St. Dev.	4	3	3	3	2	0.7	0.05	0.07	49

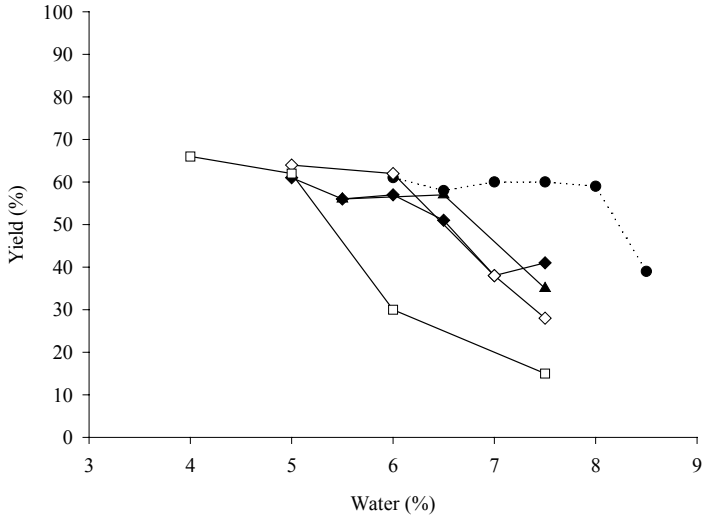


Figure 4: Influence of water concentration during extrusion on the yield of α-lactose monohydrate granules formulated without PVP (●) and with 1.25% PVP wet (▲), 2.5% PVP wet (◆), 2.5% PVP dry (◊) and 5% PVP dry (□) extruded at a screw speed of 250 rpm and a total input rate of 5.6 $kg.h^{-1}$.

not only because of the higher process efficiency, but also because it requires a considerably lower amount of liquid for the granulation process.

PVP addition had an important effect on the performance of both techniques. When, at a water concentration during extrusion of 7.5% increasing concentrations of PVP were added to the α-lactose monohydrate, the yield gradually decreased to less than 15% at 5% PVP (Fig. 4). Varying the water concentration at the different PVP concentration revealed that the optimal water concentration during extrusion decreased with increasing PVP concentration: 5.5 to 6.5%, 5.5 to 6.5% and 4 to 5% for 1.25, 2.5 and 5% PVP, respectively (Fig. 4). The possibility of wet granulation using extrusion at a considerable lower water concentration when PVP is added can be explained by the lubricating activity of PVP, resulting in a reduction of frictional forces and heat generated during granulation, as well as the binding capacities of PVP.

For high shear granulation, different PVP concentrations were not tested, but the addition of 2.5% PVP dramatically increased the yield at all water concentrations tested. However, only at 10% water a yield of ± 50% was obtained (Fig. 5). When comparing the granulation efficiency it can be concluded that for high shear granulation of α-lactose monohydrate the

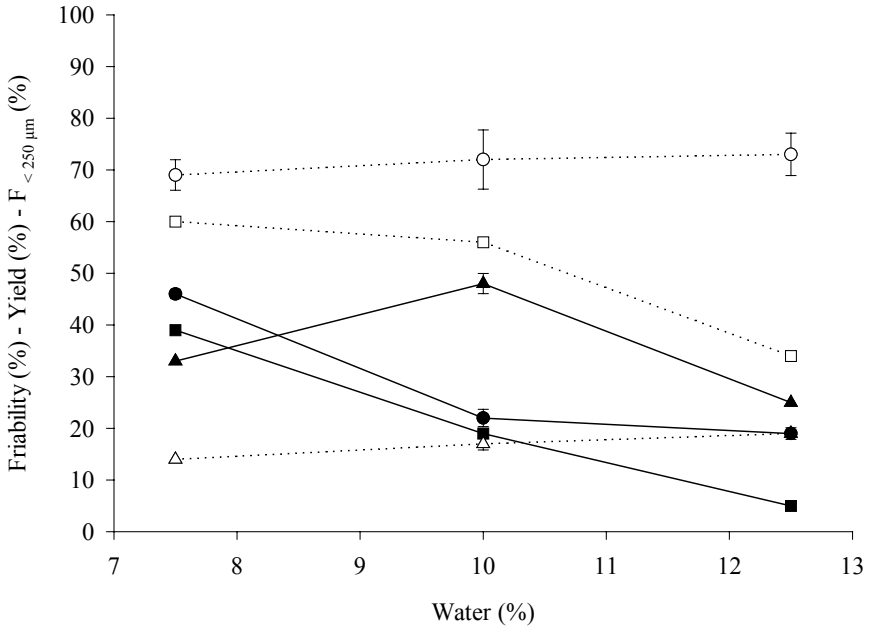
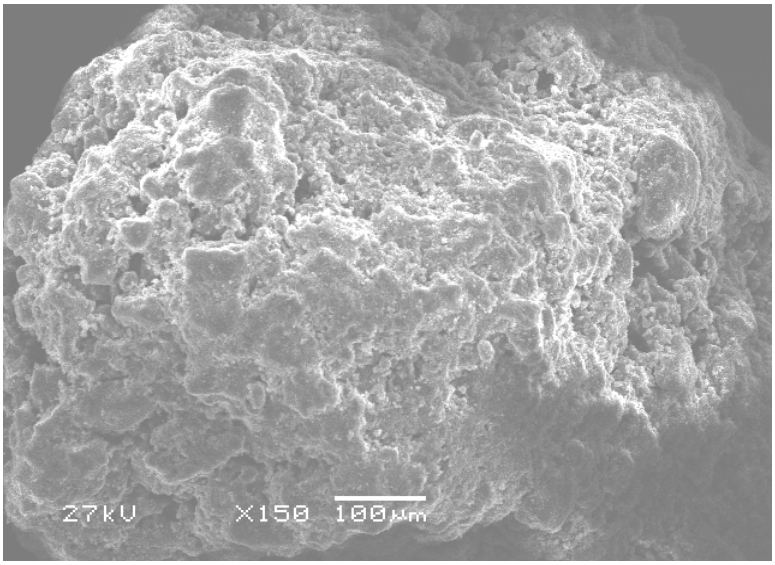


Figure 5: Influence of water concentration during high shear granulation on the granule properties of α-lactose monohydrate granules formulated without PVP and with 2.5% PVP wet at 500 rpm impeller speed and 3000 rpm chopper speed. Granule friability (o) without PVP and (●) with PVP, yield (Δ) without PVP and (▲) with PVP and fines (□) without PVP and (■) with PVP.

addition of PVP and a higher water concentration was required compared to extrusion. This difference can be attributed to the different way the binding liquid was added and to the higher densification during twin screw extrusion (Kristensen et al., 1985). These data indicated that twin screw extrusion is more efficient as a wet granulation technique for α-lactose monohydrate than high shear granulation.

Fig. 6 shows SEM pictures taken from dried granules ($F_{250\text{-}1000\ \mu m}$) produced by extrusion at reference conditions. The surface of the granules produced without PVP was rather smooth and the individual particles could not be clearly identified (Fig. 6a), possibly due to the partial dissolution of α-lactose monohydrate particles as a result of the high shearing forces during extrusion. When examining the granules with 2.5% PVP the original particles were still discernible (Fig. 6b). Similar observations were made for granules prepared using high shear granulation (Fig. 7) with the exception that these granules appeared more porous.

a



b

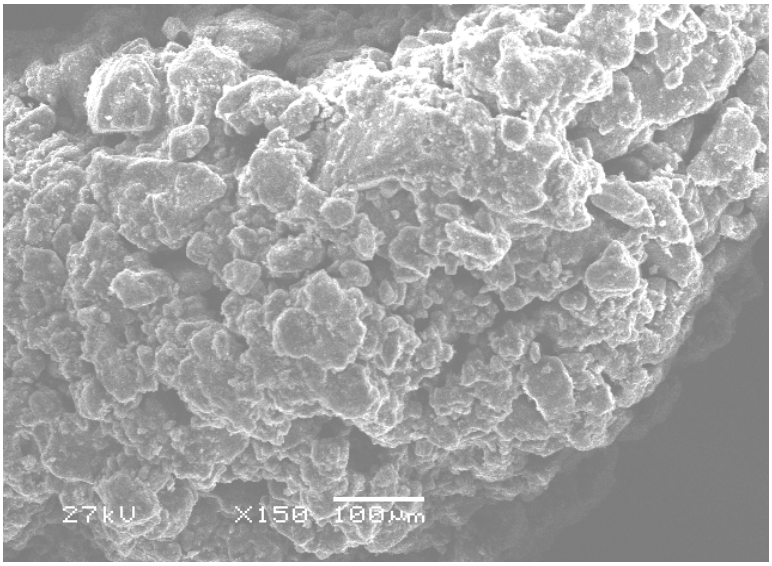
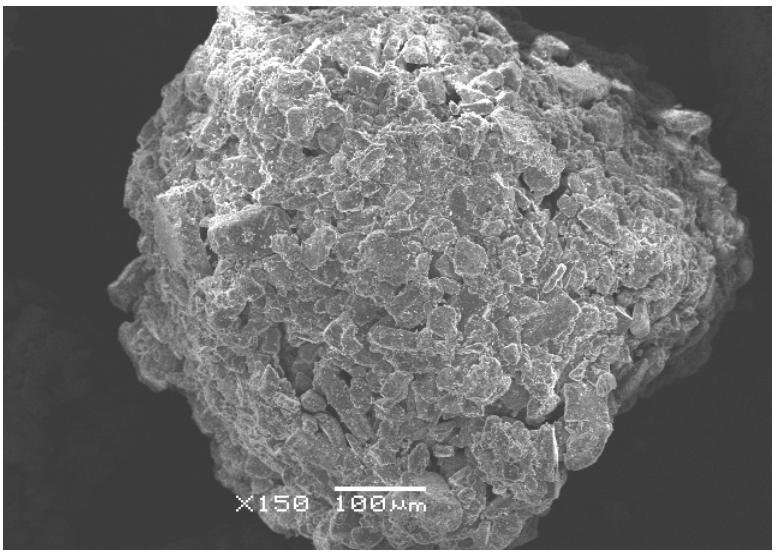


Figure 6: Scanning electron micrographs of α-lactose monohydrate granules produced by extrusion at reference conditions (7.5% water concentration, 250 rpm screw speed and 5.6 $kg.h^{-1}$ total input rate).

a. Without PVP b. With PVP (2.5% w/w, wet)

a



b

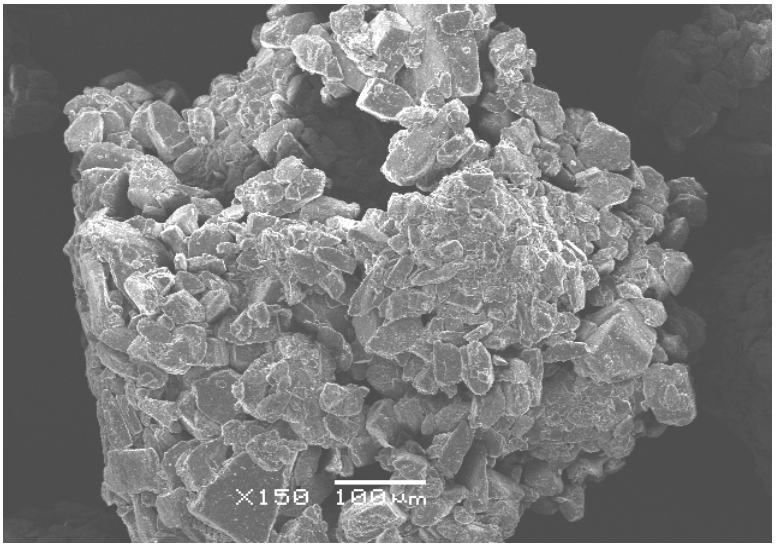


Figure 7: Scanning electron micrographs of α-lactose monohydrate granules produced by high shear granulation at 10% water, 500 rpm impeller speed and 3000 rpm chopper speed.

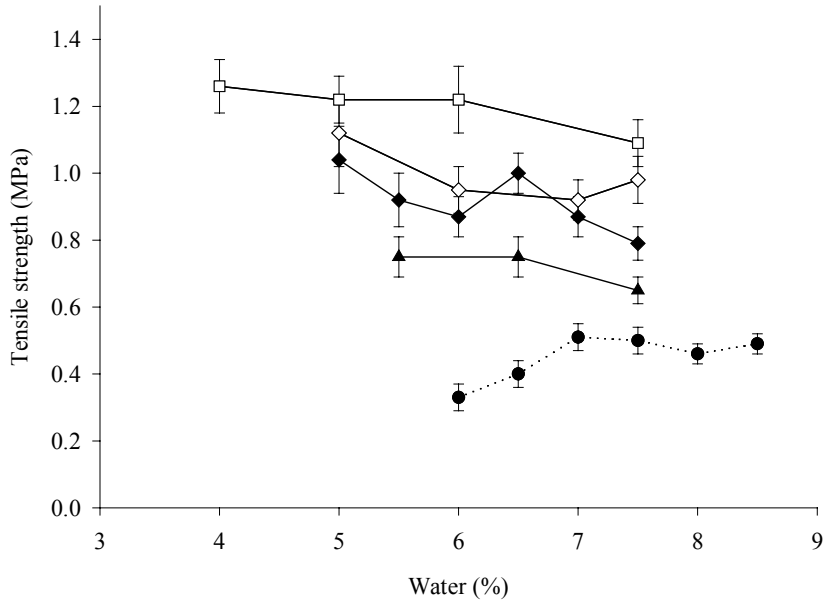
a. Without PVP b. With PVP (2.5% w/w, wet)

The porosity was measured for the granules produced by extrusion at reference conditions and ranged between 5.8 and 7.5%, independent of the PVP concentration. The porosity of granules produced using high shear granulation at 7.5% water and 500 rpm impeller speed ranged between 49.7 and 40.4% for formulations with and without PVP, respectively, which confirms the SEM observations. The difference in porosity can be explained by the different degree of densification of both techniques.

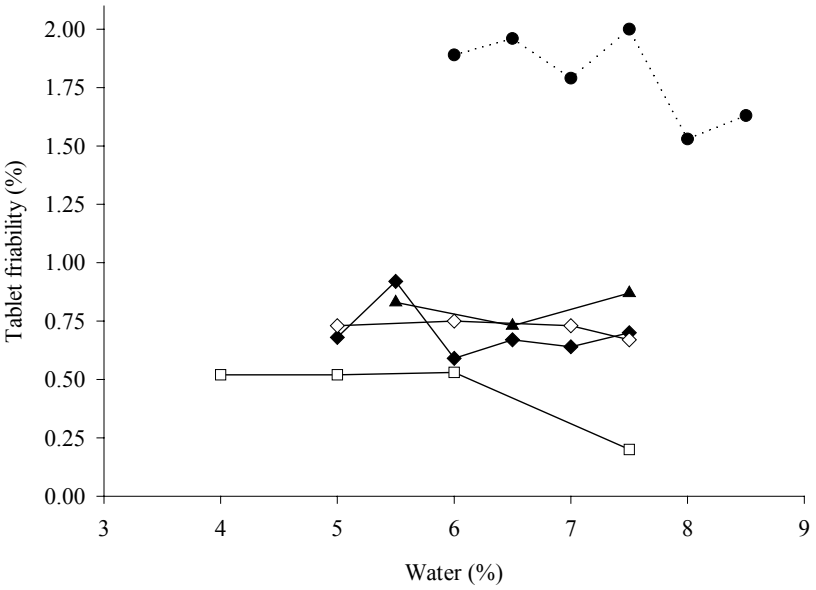
The influence of water and PVP concentration on the properties of granules prepared using twin screw extrusion was investigated. Although optimizing the water concentration during extrusion is important for the performance of the process and to ensure an acceptable yield, it did not have an important influence on the other granule properties. The compressibility never exceeded 15%, indicating the good flowability of the granules (Railker et al., 2000). The friability of the granules increased with increasing water concentration, but remained below 30%. The high yield and the low granule friability are probably due to the higher densification of the wet mass during extrusion, thereby ensuring a good distribution of granulation liquid and increasing the contact area between the individual particles which allows more bonds to be formed. PVP addition did not significantly affect the granule properties prepared by extrusion at all concentrations tested. α-Lactose monohydrate granules produced without PVP by high shear showed a higher granule friability (> 60%), a lower yield (< 20%), a higher fraction of fines ($F_{< 250\ \mu m}$) (> 35%) and a higher compressibility (< 20%) than those prepared by extrusion (Fig. 5). The granules containing 2.5% PVP produced by high shear granulation at a water concentration of 10% showed similar properties (Fig. 5) as those prepared by extrusion at the respective optimum water concentration (5.5 to 6.5%).

The influence of the water concentration during extrusion and of PVP concentration on the tablet properties is shown in Fig. 8 a, b and c. Increasing the water concentration during extrusion tended to decrease the friability of tablets formulated without PVP and resulted in a significant, though not important, increase in tablet tensile strength. The addition of PVP (1.25%) decreased the tablet friability to less than 1%, while the tablet tensile strength significantly increased to about ± 0.7 MPa and the disintegration time to more than 6 min. Increasing the PVP concentration to 5% resulted in a significant increase of tablet tensile strength and disintegration time. In view of the tablet tensile strength and friability, at least 1.25% PVP was required during granulation of α-lactose monohydrate using extrusion.

a


Tensile strength (MPa)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
3
4
5
6
7
8
9
Water (%)

b


Tablet friability (%)
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
3
4
5
6
7
8
9
Water (%)

c

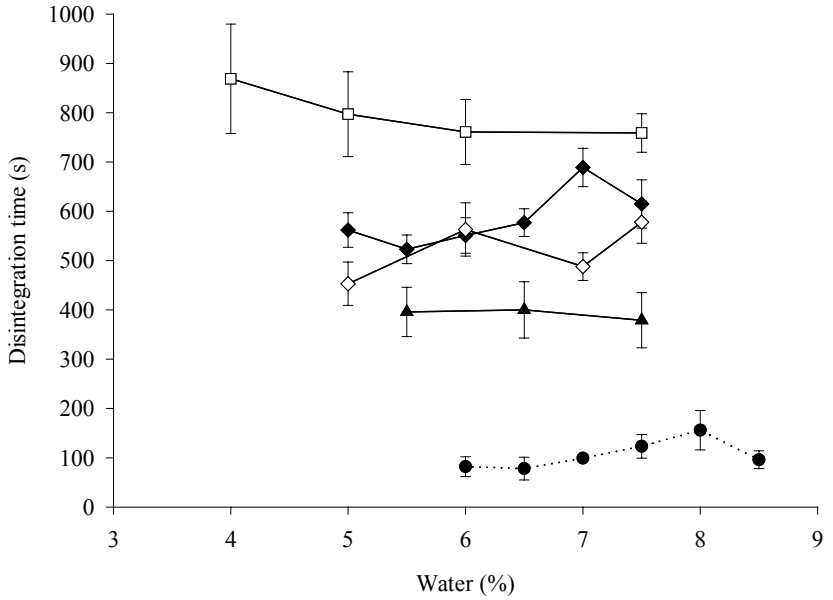


Figure 8: Influence of water concentration during extrusion on the properties of α-lactose monohydrate tablets formulated without PVP (●) and with 1.25% PVP wet (▲), 2.5% PVP wet (◆), 2.5% PVP dry (◊) and 5% PVP dry (□) extruded at 250 rpm screw speed and 5.6 $kg.h^{-1}$ kg/h total input rate. (a) Tablet tensile strength (b) Tablet friability and (c) Disintegration time.

However, it should be stressed that PVP addition was not required to achieve a high yield, whereas, at least 2.5% PVP was required for the high shear granulation of α-lactose monohydrate. Although without PVP good tablet properties were obtained from granules prepared by high shear, the yield of this granulation technique for pure α-lactose monohydrate was too low.

Comparison of the properties of the tablets prepared from granules produced by high shear granulation (Fig. 9) with those obtained by extrusion revealed that tablets from granules prepared by high shear showed a significant higher tensile strength and faster disintegration time for the formulations without as well as with PVP.

When comparing the granule and tablet properties obtained for both methods of PVP addition no significant differences were observed, except for the tablet disintegration time at a water concentration of 5% during extrusion.

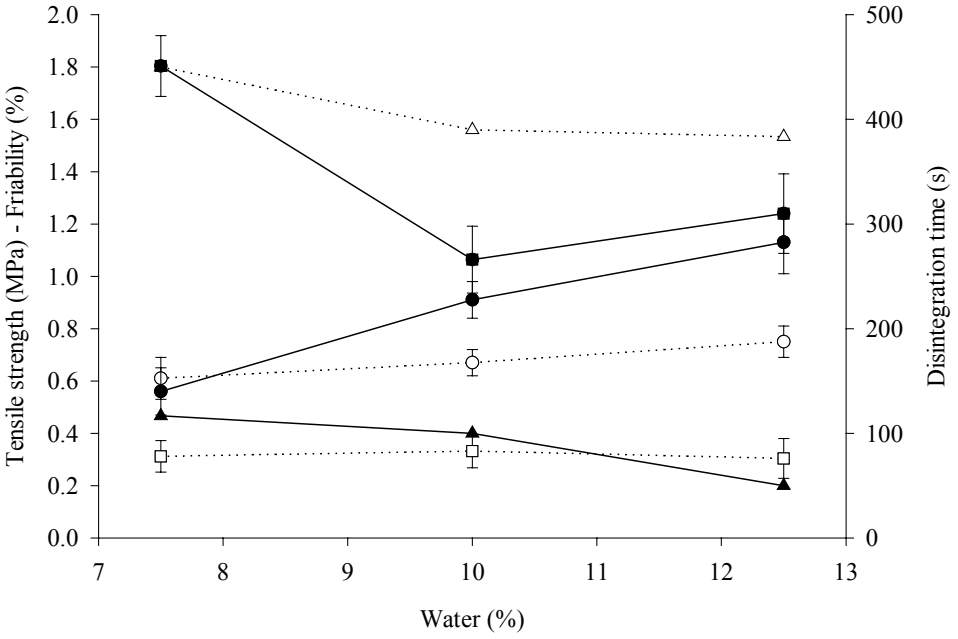


Figure 9: Influence of water concentration during high shear granulation on the properties of tablets prepared from α-lactose monohydrate granules formulated without PVP and with 2.5% PVP wet at 500 rpm impeller speed and 3000 rpm chopper speed. Tablet tensile strength (o) without PVP and (●) with PVP, friability (Δ) without PVP and (▲) with PVP and disintegration time (□) without PVP and (■) with PVP.

The average $t_{90\%}$ dissolution time of the tablets (with 2.5% PVP) containing hydrochlorothiazide was 25 ± 1 min and complied with the USP XXIII monograph requiring that not less than 60% of the drug is dissolved within 60 min.

Variation of the screw speed and the total input rate clearly affected the process feasibility. Combining a low screw speed with a high total input rate led to increased friction, whereas a too low total input rate resulted in insufficient filling of the extruder barrel (Fig. 3b). Changing the screw speed from 200 to 450 rpm did not influence the granule nor the tablet properties, with the exception of the granule friability which significantly increased (but remained below 30%) with increasing screw speed. The total input rate did not significantly influence the granule and tablet properties. Thus optimizing the screw speed and the total input rate is required for the feasibility of the process, however, these parameters have a limited impact on the granule and tablet properties.

3.6 Conclusion

It can be concluded that twin screw extrusion is a suitable alternative for the wet granulation of α-lactose monohydrate. Optimizing the process parameters and the water concentration are required to obtain an acceptable yield, but they had no important effect on the granule or tablet properties. Although good granule properties were obtained without PVP, the addition of PVP was required to improve tablet properties. In contrast to extrusion, high shear granulation did not allow granulation without PVP and required a higher water concentration for the granulation of formulations containing PVP. It can be concluded that the technique of extrusion granulation is more efficient as granulation technique than high shear granulation. Besides it has the advantage of allowing semi-continuous granulation. Further experiments will be performed in order to adapt the process so that the wet sieving step is not required, thus obtaining a fully continuous process.

3.7 References

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4 Extrusion/granulation and high shear granulation of different grades of lactose and highly dosed drugs: a comparative study

Accepted for publication in Drug Dev. Ind. Pharm.

4.1 Introduction

In the pharmaceutical industry the choice of a suitable granulation process depends, to some extent, on the physical properties of the powders to be granulated and on the requirements of the final granules. The physical characteristics of granules, such as particle size distribution, friability and porosity, are of interest as they will affect the down stream processes. The granulation technique as well as the processing parameters employed during granulation have a significant effect on the granule characteristics, hence the properties of the tablets prepared from the granules. In addition the physical properties of the raw materials will also affect the granulation process as well as the granule properties. A granulation technique that allows to level out any differences that might exist between the starting materials would therefore be of interest.

Extrusion/granulation is a semi-continuous wet granulation technique, which was shown to be more efficient for the granulation of α-lactose monohydrate 200M than conventional high shear granulation (Keleb et al., 2002). The aim of this study was to evaluate the robustness of the extrusion/granulation process using different lactose grades to examine the influence of lactose particle size and morphology on the granulation process and on the granule and tablet properties in comparison with high shear granulation. In addition the feasibility of processing formulations containing a high concentration of a drug having poor compaction properties (paracetamol) or having poor flow and disintegration properties (cimetidine) was evaluated.

4.2 Materials

The different grades of lactose used were: crystalline α-lactose monohydrate (Pharmatose® 450M, 200M, 100M, 90M) and anhydrous β-lactose (Pharmatose® DCL 21) (DMV, Veghel, The Netherlands). The physical properties of the lactose grades are listed in Table 1. Paracetamol was received from Mallinckrodt (Capitol Boulevard, NC, USA) and cimetidine was purchased from Roig Farma (Barcelona, Spain). Polyvinylpyrrolidone (PVP, Kollidon®

K30) and crospovidone (Kollidon® CL) were received from BASF (Ludwigshafen, Germany).

Table 1: The physical properties of different grades of lactose.

Grade	Particle size* (μm)	Morphology	Bulk density (g/cm^3)	Solubility
α-Lactose monohydrate 90M	135	non-granular	0.76	1 in 5
α-Lactose monohydrate 100M	130	non-granular	0.75	1 in 5
α-Lactose monohydrate 200M	40	non-granular	0.55	1 in 5
α-Lactose monohydrate 450M	20	non-granular	0.47	1 in 5
Anhydrous β-lactose	150	granular	0.67	1 in 2.2

*Average particle size by sieving (certificate of analysis, DMV)

4.3 Methods

4.3.1 Extrusion/granulation

Granulation was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1 and equipped with a standard screw profile with two mixing sections and a die block. The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the extruder barrel using a peristaltic pump (Watson Marlow, Cornwall, UK). Granulation was carried out at 25°C barrel temperature, 250 rpm screw speed, 5.6 $kg.h^{-1}$ total input rate and 7.5% (w/w) water content during extrusion. If required, crospovidone, paracetamol or cimetidine were blended before granulation with α-lactose monohydrate for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). Extrudates were collected 10 min after the granulation was started in order to allow the system to equilibrate, then the extrudates (400 g) were immediately wet sized using a 1 mm oscillating sieve (Frewitt, Fribourg, Switzerland), operated at a minimal distance between rotor and sieve (Keleb et al., 2002). The wet granules were oven-dried at 25°C for 20 h. All water concentrations were based on the wet mass, whereas PVP, crospovidone, cimetidine and paracetamol concentrations were based on dry weight.

The extrusion granulation process was evaluated by monitoring power consumption and barrel temperature. If the power consumption exceeded 80% of the maximum capacity the process was stopped in order to avoid machine damage.

4.3.2 High shear granulation

The granulation was performed in a high shear granulator (Gral 10, Machines Collette, Wommelgem, Belgium) at 500 rpm impeller speed, 3000 rpm chopper speed and 10% (w/w) water concentration. If required, crospovidone, paracetamol or cimetidine were blended before granulation with α-lactose monohydrate for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). The granulation liquid (pure water or an aqueous PVP solution) was added using a peristaltic pump (Watson Marlow, Cornwall, UK). After a 2 min mixing period of the powder, the required amount of granulation liquid was continuously added over a period of 10 min. Wet massing was continued for 2 min following complete liquid addition. The wet granules were oven-dried at 25°C for 20 h.

4.3.3 Compression of tablets

The same method as described in Chapter 3 was used to manufacture the tablets.

4.3.4 Granule evaluation

The same methods as described in Chapter 3 were used to determine the yield of the process and the particle size, friability and density (bulk and tapped) of the granules.

4.3.5 Tablet evaluation

The same methods as described in Chapter 3 were used to determine the friability, tensile strength and disintegration time of the tablets.

4.3.5.1 Tablet porosity

The tablet skeletal volume was determined (n=10) using He-pycnometry (Micromeritics, Norcross, GA, US) and the dimensions of the tablet were measured using a micrometer from which the bulk volume was calculated. The tablet porosity ε was determined (n=3) by the following equation $\varepsilon = ((\text{bulk volume} - \text{skeletal volume})/ \text{bulk volume}) * 100$.

4.3.5.2 Dissolution test

Dissolution tests on paracetamol tablets were performed in 900 ml phosphate buffer (pH 5.8) using the paddle method (Vankel, Cary, NC, US). The dissolution medium was maintained at

37 ± 0.5°C, while the rotation speed was set at 50 rpm (USP XXIV). Samples (5 ml) were withdrawn after 5, 10, 15, 20, 25 and 30 min and concentrations were spectrophotometrically determined at 243 nm (Lambda 12 Perkin Elmer, Norwalk, US). Similarly dissolution tests were performed on cimetidine tablets in 900 ml water using the basket method (Vankel, Cary, NC, US). The dissolution medium was maintained at 37 ± 0.5°C, while the rotation speed was set at 100 rpm (USP XXIV). Samples (5 ml) were withdrawn after 3, 6, 9, 12 and 15 min and concentrations were spectrophotometrically determined at 218 nm (Lambda 12 Perkin Elmer, Norwalk, US).

4.4 Statistical analysis

Statistical analysis was performed using the computer program SPSS version 11.0.
The influence of lactose particle size, particle morphology, composition, storage conditions and granulation technique on granule friability, tablet tensile strength and disintegration time was analysed using one-way ANOVA. For further comparison a multiple comparison among pairs of means was performed using the Scheffé test with $P < 0.05$ as a significance level. The data were tested for normal distribution with a Kolmogorov-Smirnov test and the homogeneity of variances was tested with the Levene's test.

4.5 Results and discussion

4.5.1 Granulation of different lactose grades

Extrusion/granulation of the different grades of α-lactose monohydrate (without PVP) resulted in a similar barrel temperature and power consumption as shown in Table 2. For formulations with PVP the barrel temperature and power consumption decreased as lactose particle size increased due to the decrease in particle surface area which resulted in improved particle lubrication. All particle sizes were processed smoothly, except for α-lactose monohydrate 90M as its larger particle size resulted in high frictional forces. Extrusion/granulation of anhydrous β-lactose was associated with a remarkable increase in barrel temperature and in power consumption mainly because its granular particles have a hard and irregular structure.

Besides it should be reported that although α-lactose monohydrate 200M was fed smoothly using a double screw feeder to transport the powder into the extruder barrel (Keleb et al., 2002), other lactose grades having a larger or smaller particle size exhibited some problems during feeding. A gradual decrease in feed rate and difficulties with the screw rotation of the feeder (or even blocking of the screw movement) were observed for α-lactose monohydrate 100M, 90M and anhydrous β-lactose. α-Lactose monohydrate 450M tended to adhere to the hopper surface, mainly due to the cohesiveness of its particles. These feeding problems did not hamper obtaining accurate feeding rates during short term experiments, but could cause inaccurate feeding rates during longer processing times. There is a need for the selection of adequate feeding systems in order to allow a broad range of materials with different flow properties to be easily processed.

Table 2: Process parameters during extrusion/granulation of different lactose grades.

PVP *(%)*	**Temperature** *(°C)*	**Power consumption** *(%)*
α-Lactose monohydrate 450M		
0	44	27
2.5	40	29
α-Lactose monohydrate 200M		
0	42	26
2.5	35	24
α-Lactose monohydrate 100M		
0	36	28
2.5	29	21
α-Lactose monohydrate 90M		
0	39	20
2.5	29	17
Anhydrous β-lactose		
0	58	72
2.5	50	65

During extrusion/granulation optimisation of the water concentration was essential for processing as well as for obtaining good granule properties. The water concentration was optimised in a previous study for α-lactose monohydrate 200M (Keleb et al., 2002) and this

water concentration was used for the granulation of all grades of lactose. The particle size of lactose did have an influence on the optimal water concentration, which can be explained by the different viscoelastic properties of the wet mass, affecting extrudability, agglomeration as well as wet sieving (Kleinebudde and Lindner, 1993; Keleb et al., 2002).

During extrusion/granulation of anhydrous β-lactose and α-lactose monohydrate 90M at reference water concentration a lower yield was obtained for the latter and a further reduction of the water concentration was required. Anhydrous β-lactose has a higher solubility and according to Lustig-Gustafsson (1999) a lower water concentration will be required for successful granulation. However, α-lactose monohydrate 90M required less water than anhydrous β-lactose. This difference is probably due to the differences in surface area and powder bed porosity.

Table 3: The granule properties of the different lactose grades processed by extrusion/granulation and high shear granulation

PARAMETERS	GRANULE PROPERTIES							
Lactose type	**PVP** *(%)*	**Water** *(%)*	**Friability** *(%)*	**Yield** *(%)*	**Particle size distribution** *<250 µm*	*250-1000 µm*	*>1000 µm*	**Compressibility** *(%)*
Extrusion/granulation								
α-lactose monohydrate 90M	0	7.5	32	34	46	49	5	9
α-lactose monohydrate 100M	0	7.5	22	54	24	65	11	12
α-lactose monohydrate 200M	0	7.5	17	60	26	63	11	11
α-lactose monohydrate 450M	0	7.5	20	58	17	61	22	14
Anhydrous β-lactose	0	7.5	23	59	26	61	14	13
α-lactose monohydrate 90M	2.5	7.5	15	17	13	75	12	15
α-lactose monohydrate 90M	2.5	6.5	23	33	14	76	10	15
α-lactose monohydrate 100M	2.5	7.5	13	41	19	78	2	13
α-lactose monohydrate 100M	2.5	6.5	16	51	29	65	5	15
α-lactose monohydrate 200M	2.5	7.5	20	41	15	73	12	14
α-lactose monohydrate 200M	2.5	6.5	16	52	29	65	5	15
α-lactose monohydrate 450M	2.5	7.5	19	33	22	59	19	14
Anhydrous β-lactose	2.5	7.5	8	61	23	63	14	13
High shear granulation								
α-lactose monohydrate 90M	0	10	84	32	34	52	14	16
α-lactose monohydrate 100M	0	10	91	33	33	56	10	16
α-lactose monohydrate 200M	0	10	72	17	56	32	12	10
α-lactose monohydrate 450M	0	10	52	24	44	47	12	15
Anhydrous β-lactose	0	10	81	38	55	42	4	15
α-lactose monohydrate 90M	2.5	10	15	20	10	64	27	14
α-lactose monohydrate 100M	2.5	10	17	25	7	72	20	14
α-lactose monohydrate 200M	2.5	10	22	48	19	69	12	14
α-lactose monohydrate 450M	2.5	10	28	30	38	53	9	15
Anhydrous β-lactose	2.5	10	27	51	37	58	5	13

Comparison of the optimal water concentration for the two different granulation techniques showed that extrusion/granulation required a lower water concentration than high shear granulation. The properties of granules produced by extrusion/granulation and high shear granulation are shown in Table 3. For extrusion/granulation and high shear granulation the particle size affected the granule properties. For formulations without PVP a significantly higher friability was obtained for α-lactose monohydrate grades having a larger particle size.

Table 4: The properties of tablets prepared by compression of different lactose grades processed by extrusion/granulation and high shear granulation.

PARAMETERS			**TABLET PROPERTIES**		
Lactose *grade*	**PVP** *(%)*	**Water** *(%)*	**Tensile strength** *(MPa)*	**Friability** *(%)*	**Disintegration** *(s)*
Extrusion/granulation					
α-lactose monohydrate 90M	0	7.5	0.75	1.7	164
α-lactose monohydrate 100M	0	7.5	0.47	1.9	192
α-lactose monohydrate 200M	0	7.5	0.50	1.9	123
α-lactose monohydrate 450M	0	7.5	0.32	2.2	189
Anhydrous β-lactose	0	7.5	0.88	1.1	348
α-lactose monohydrate 90M	2.5	7.5	1.11	0.7	648
α-lactose monohydrate 90M	2.5	6.5	0.99	0.8	589
α-lactose monohydrate 100M	2.5	7.5	0.75	0.9	697
α-lactose monohydrate 100M	2.5	6.5	1.00	0.7	577
α-lactose monohydrate 200M	2.5	7.5	0.97	0.7	615
α-lactose monohydrate 200M	2.5	6.5	1.04	0.7	577
α-lactose monohydrate 450M	2.5	7.5	1.12	0.6	594
Anhydrous β-lactose	2.5	7.5	1.26	0.7	299
High shear granulation					
α-lactose monohydrate 90M	0	10	0.13	2.9	66
α-lactose monohydrate 100M	0	10	0.15	2.7	116
α-lactose monohydrate 200M	0	10	0.67	1.7	83
α-lactose monohydrate 450M	0	10	0.28	1.7	112
Anhydrous *β*-lactose	0	10	0.59	1.2	163
α-lactose monohydrate 90M	2.5	10	0.32	0.9	417
α-lactose monohydrate 100M	2.5	10	0.31	1.2	360
α-lactose monohydrate 200M	2.5	10	0.91	0.8	266
α-lactose monohydrate 450M	2.5	10	0.51	0.6	373
Anhydrous β-lactose	2.5	10	0.73	0.7	286

The lower yield for α-lactose monohydrate grades with a larger particle size is in agreement with the data of Mackaplow et al. (2000) who found that granulation of α-lactose monohydrate with a large particle size yielded weak granules. This was explained by the fact that water did not provide the necessary strength to the agglomerates and breakage would often dominate due to the low agglomerate strength.

Comparison of extrusion/granulation with high shear granulation showed that the former resulted in a significantly lower granule friability and a higher yield.

Table 4 shows the properties of tablets produced from granules prepared by extrusion granulation and high shear granulation.

The particle size of α-lactose monohydrate did affect tablet tensile strength after extrusion/granulation. The properties of tablets obtained after high shear granulation were more affected by particle size as an effect on both tensile strength and disintegration time was observed.

In contrast to the lactose particle size, the lactose grade has a similar effect on the tablet properties obtained by both techniques. Tablets prepared from anhydrous β-lactose exhibited a significantly higher tensile strength and a lower friability than those prepared from α-lactose monohydrate 90M, irrespective of the granulation technique used. This is probably due to the higher compactability of anhydrous β-lactose.

The tablet properties obtained from granules compressed after extrusion/granulation showed a significantly higher tensile strength compared to the high shear prepared granules, indicating that extrusion/granulation resulted in improved tablet properties.

4.5.2 Granulation of paracetamol

During extrusion/granulation of all formulations containing paracetamol a similar barrel temperature and power consumption was recorded. The barrel temperature and the power consumption varied between 31 and 39°C and between 21 and 29%, respectively. All paracetamol formulations without PVP showed no problems during wet sieving, while at a 7.5% water concentration the extrudates (containing 2.5% PVP) stuck to the sieve during wet sizing and the water concentration had to be lowered in order to solve the problem (Keleb et al., 2002). High shear granulation of pure paracetamol without PVP was not possible, even at higher water concentrations.

Table 5: Influence of granulation technique on the granule and tablet properties of paracetamol formulations.

Processing variables			**Granule properties**						**Tablet properties**		
Paracetamol	**Water**	**PVP**	**Friability (%)**	**Yield (%)**	**Particle size analysis**			**Compressiblilty**	**Tensile strength**	**Friability**	**Disintegration**
(%)	(%)	(%)	***250-1000 µm***	***(%)***	***<250µm***	***250-1000µm***	***>1000µm***	***(%)***	***MPa***	***(%)***	***(s)***
Extrusion/granulation											
20	7.5	0	27	34	27	37	36	13	0.53	2.5	115
40			34	42	38	47	15	12	0.56	3.0	422
60			39	40	38	43	19	12	0.60	3.3	1157
80			50	39	41	41	18	13		poor compatibility	
100			76	36	41	39	20	11		poor compatibility	
20	7.5	2.5	30	19	26	69	5	14	1.06	1.2	636
40			32	20	11	66	26	14	0.96	1.4	906
60			33	20	21	58	21	14	0.96	1.7	1023
80			30	20	31	48	21	10	0.95	1.9	1712
97.5			42	20	28	40	32	11	1.12	1.9	3299
92.5*											
High shear granulation											
20	10	0	66	30	27	52	21	14	0.38	2.8	93
40			61	34	20	65	15	12	0.36	15.0	476
60			61	30	16	67	17	13		poor compatibility	
80			61	32	18	66	16	12		poor compatibility	
100					Granulation not possible						
20	10	2.5	21	42	7	70	25	13	0.95	1.1	359
40			18	24	5	66	29	8	0.82	1.6	1071
60			32	18	3	63	34	10	0.71	2	1489
80			22	16	8	65	27	14	0.75	2.2	2799
97.5			33	16	6	65	29	11		poor compatibility	

*Formulation containing 5% crospovidone

Table 5 shows the properties of paracetamol granules prepared by extrusion/granulation and high shear granulation. Extrusion/granulation without PVP resulted at all paracetamol concentrations in a yield of about 40%. At 20% paracetamol a granule friability of 27% was obtained. However, the friability significantly increased as the paracetamol concentration increased, reaching 76% for pure paracetamol granules. This trend in the friability data was directly correlated with the gradual decrease of α-lactose monohydrate present in the granules. All granules without PVP obtained by high shear granulation showed a significantly higher granule friability and a lower yield than those prepared by extrusion/granulation. Although extrusion/granulation showed a higher efficiency than high shear granulation, it failed to produce good quality paracetamol granules without PVP.

Addition of 2.5% PVP at reference water concentration only significantly improved the friability at a paracetamol concentration above 80%, but resulted in a markedly lower yield. For high shear granulation, addition of PVP always resulted in a significant decrease of the friability, while the effect on the yield depended on the drug concentration. The yield gradually decreased as the paracetamol concentration increased due to an increasing amount of lumps formed at higher paracetamol concentration.

The compressibility of all formulations ranged between 8 and 14%, indicating the good flow properties of the granules, irrespective of the granulation technique.

From these results it is obvious that extrusion/granulation is more efficient than high shear granulation for the granulation of paracetamol.

Table 5 also shows the properties of tablets containing different concentrations of paracetamol prepared by extrusion granulation and high shear granulation. For tablets compressed from granules prepared by extrusion/granulation a tendency for capping and lamination was observed at paracetamol concentration above 80%. Tablets without PVP containing up to 60% paracetamol had a tensile strength below 0.59 MPa.

For tablets prepared from granules without PVP produced by high shear granulation the tendency for capping and lamination was already observed at 60% paracetamol, while tablets containing up to 40% paracetamol had a tensile strength below 0.38 MPa. Those results are in agreement with Becker et al. (1997) who reported that paracetamol tablets produced without binder have a low strength.

Addition of PVP allowed to prepare tablets containing a higher paracetamol concentration and yielded stronger tablets.

It is obvious that it was possible to prepare tablets from paracetamol granules containing only drug and 2.5% PVP (and no lactose) when extrusion/granulation was used, whereas no tablets were obtained from this formulation using high shear granulation. Although addition of PVP resulted in a considerable reduction of the tablet friability it remained above 1%.

Similar disintegration times for tablets prepared by extrusion/granulation and high shear granulation were obtained. Increasing the paracetamol concentration resulted in a significant increase in the disintegration time. For paracetamol tablets (without PVP) prepared by both techniques, only those containing 20% paracetamol, complied with the requirements of the US pharmacopoeia (80% paracetamol released within 30 min). The results of the dissolution experiments on paracetamol tablets with PVP are shown in Fig. 1. Addition of PVP dramatically enhanced the dissolution rate of paracetamol tablets. This effect can be attributed to the interaction of PVP with paracetamol due to the formation of hydrogen bonds (Garekani, 1996).

Comparison of the dissolution of paracetamol tablets obtained by both processes clearly showed that tablets prepared from granules obtained by extrusion/granulation showed a faster dissolution than those obtained by high shear granulation. For tablets containing 97.5% paracetamol produced via extrusion/granulation the dissolution profiles did not comply with the pharmacopoeial requirements. However, after the addition of 5% crospovidone a fast dissolution rate was obtained.

These results indicated that extrusion/granulation allowed to obtain tablets with a higher paracetamol concentration and resulted in improved tablet properties in comparison with high shear granulation.

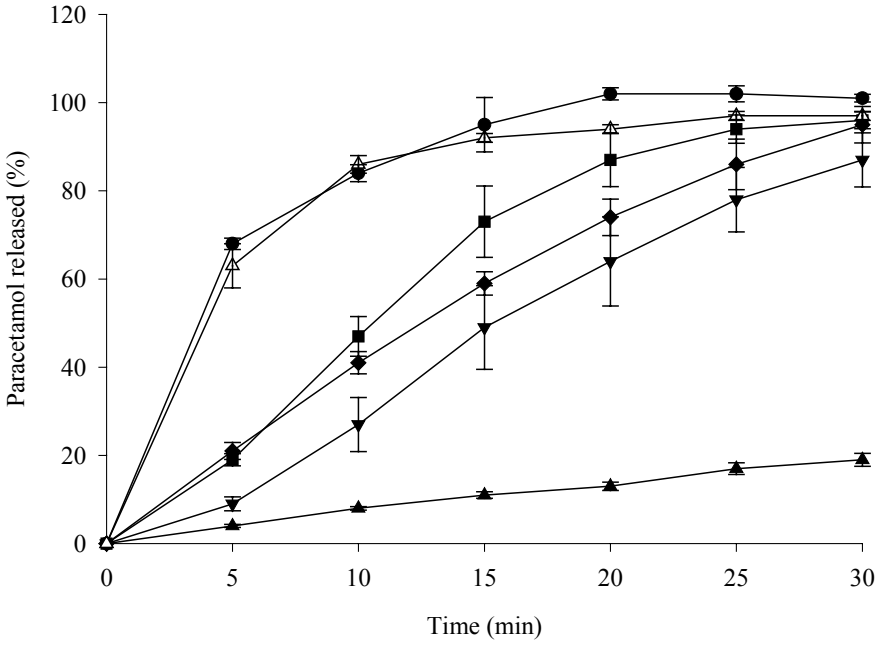

Figure1a: Dissolution profiles of tablets (with 2.5% PVP) containing 20% (●), 40% (■), 60% (♦), 80% (▼) and 97.5% (▲) paracetamol and containing 92.5% paracetamol and 5% crospovidone (△). The tablets were prepared from granules produced by extrusion/granulation.

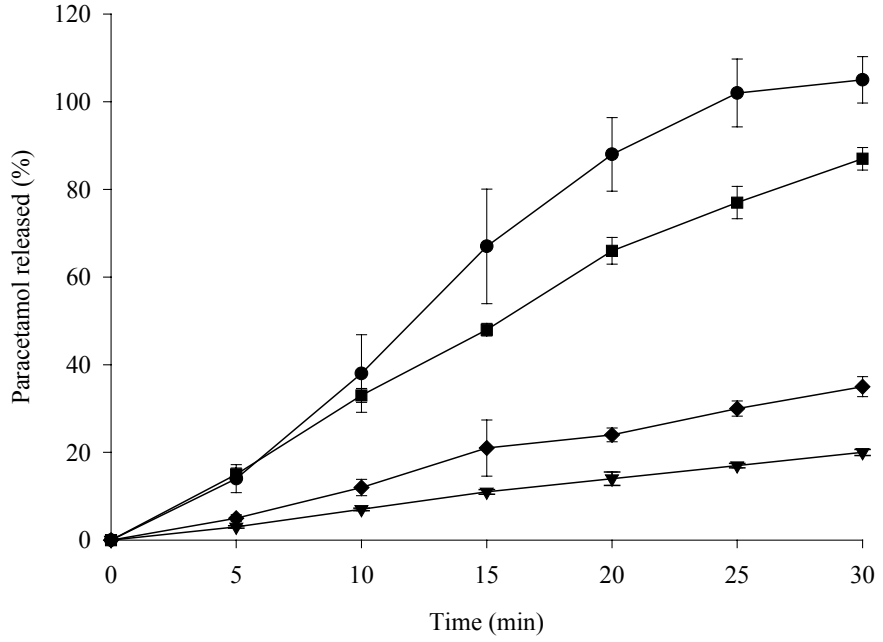

Figure 1b: Dissolution profiles of tablets (with 2.5% PVP) containing 20% (●), 40% (■), 60% (♦) and 80% (▼) paracetamol. Tablets were prepared from granules produced by high shear granulation.

4.5.3 Granulation of cimetidine

Granulation of cimetidine by extrusion/granulation at reference conditions was associated with a high barrel temperature (52-54°C) and a high power consumption (54-58%). The extrudates obtained had a rough surface and were difficult to wet size due to the hardness of the extrudates. The low water concentration in combination with the pressure exerted on the extrudates at the die block as well as the elevated barrel temperature could be responsible for the extrudate hardness. Increasing the water concentration to 17.5 and 14.5% for the formulation without and with PVP, respectively, reduced the barrel temperature to below 39°C and the power consumption to below 23%. Moreover, cimetidine extrudates produced at those water concentrations were easily wet sized.

High shear granulation of cimetidine without PVP was not feasible even at a water concentration up to 17.5%, whereas the addition of PVP allowed to process cimetidine.

Table 6 compares the properties of cimetidine granules prepared by extrusion/granulation and high shear granulation. For extrusion/granulation of cimetidine (without PVP) at reference conditions a friability of 11% and a yield of 32% were obtained. This low yield was mainly due to the hardness of the extrudates, which made it difficult to break them down into granules during wet sizing. Increasing the water concentration to 17.5% made the extrudates suitable for wet sizing and increased the yield to 62%. Addition of 2.5% PVP to cimetidine resulted in a yield of 46 and 22% and a friability of 12 and 64% for extrusion granulation and high shear granulation, respectively. The compressibility ranged between 13 and 18% for all granules produced by both techniques, indicating their good flow properties.

These results show that extrusion/granulation is far more efficient for the wet granulation of cimetidine compared to high shear granulation.

Table 6 also shows the properties of cimetidine tablets produced by extrusion/granulation and by high shear granulation. Similar tablet properties were obtained for both granulation techniques. For all tablets a friability below 1% and a tensile strength above 0.79 MPa was obtained. However, the disintegration time was above 60 min (formulations without disintegrant) and the dissolution failed to meet the US pharmacopoeia requirements. The addition of 5% crospovidone significantly reduced the disintegration time and ensured that these cimetidine formulations complied with the US pharmacopoeia dissolution requirements (60% cimetidine released within 15 min) as shown in Fig. 2.

The fact that cimetidine tablet properties are not affected by the granulation method is in contrast to paracetamol tablets where the granulation method showed to be the predominant

factor for the tablet production. This different behaviour of both drugs can be explained by their differences in compactability. Paracetamol has poor compactability properties, and therefore the tablet properties are highly dependent on the granule properties, which mainly depend on the granulation method. On the contrary, cimetidine has good compaction properties, and thus granulation had a less predominant role.

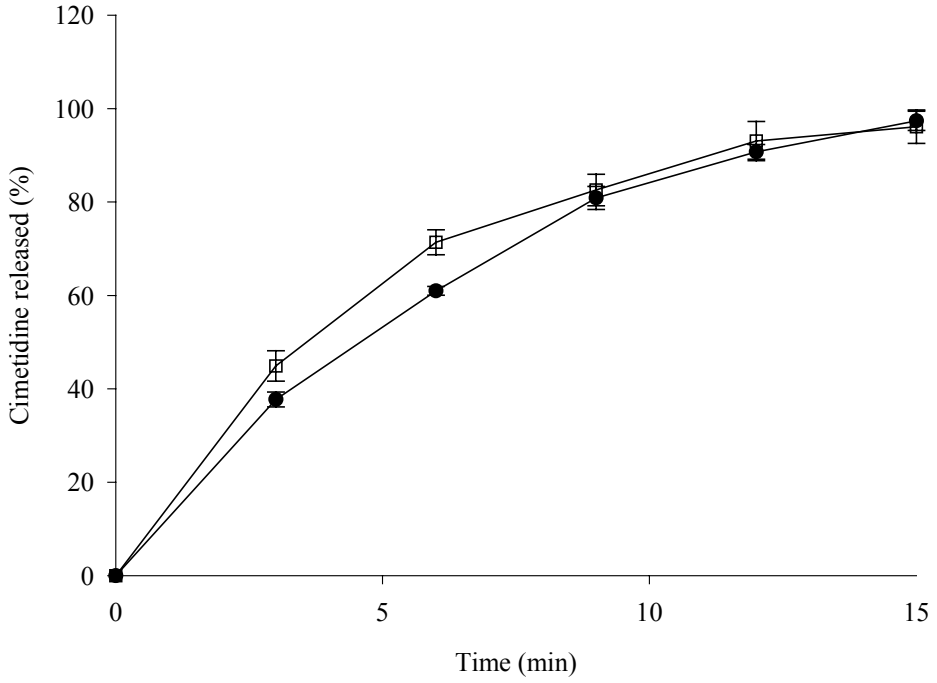

Figure 2: Dissolution profiles of tablets containing 92.5% cimetidine, 2.5% PVP and 5% crospovidone prepared by compression after extrusion/granulation (●) and after high shear granulation (□).

Table 6: Influence of granulation technique on the granule and tablet properties of cimetidine formulations.

Parameters			Granule properties						Tablet properties		
PVP	PVP-CL	Water	Friability	Yield	Particle size distribution			Compressibility	Tensile strength	Friability	Disintegration
(%)	*(%)*	*(%)*	*(%)*	*(%)*	*<250µm*	*250-1000µm*	*>1000µm*	*(%)*	*(MPa)*	*(%)*	*(s)*
Extrusion/granulation											
0	0	7.5	11	32	30	64	7	13	1.76	0.8	> 3600
2.5	0	7.5	12	46	27	67	6	14	1.86	0.7	> 3600
0	5	17.5	43	54	40	57	3	14	1.23	0.7	52
2.5	5	14.5	30	40	48	50	2	18	1.70	0.7	154
High shear granulation											
0	0	10.0					No granules obtained				
0	0	17.5					No granules obtained				
2.5	0	10.0	64	22	58	40	2	16	1.83	0.5	> 3600
2.5	5	14.5	89	9	87	13	0	18	0.93	1.3	124

4.6 Conclusion

This study showed that during granulation of different lactose grades, particle size and morphology had only a minor influence on the extrusion/granulation process, whereas significant differences were observed after high shear granulation.

On comparing granules and tablets produced by both granulation processes, materials processed by extrusion granulation showed superior properties than those granulated by high shear.

Granulation of highly dosed drugs (paracetamol or cimetidine) using extrusion/granulation was more efficient than high shear granulation, resulting in a higher yield and lower friability for a lower water concentration.

4.7 References

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5 Twin screw granulation as a simple and efficient tool for continuous wet granulation

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5.1 Introduction

Wet granulation is considered one of the most important processes in the manufacturing of solid dosage forms. Production of solid dosage forms using granules has several advantages such as enhanced flowability, improved compactability, reduced segregation and less dust. The most commonly used wet granulation techniques are high shear and fluid bed granulation.

There is an increasing need for alternative processes that are more economic, reliable and reproducible, taking into consideration the possibility of automation and process continuity. Continuous processes offer two advantages: there is no scale-up study necessary resulting in a shorter development time and a 24 h automatic production line (lights-out operation) would be possible. Recently, this subject is gaining more interest and several techniques have been reported for continuous granulation.

Leuenberger (2001) reported a quasi-continuous granulation technique using a specially designed high shear mixer/granulator, which is connected to a multicell fluid bed dryer. This technique resulted in granules of a similar or even better quality compared to those produced by conventional granulation equipment. Schroeder and Steffens (2002) used a modified planetary roller extruder for continuous wet granulation. Lindberg et al. (1987 and 1988) were the first to report on the possibility of using a twin screw extruder for the continuous granulation of an effervescent paracetamol preparation. However, no data were presented on the suitability of these granules for compaction. In 1993, Kleinebudde and Lindner studied the twin screw extrusion process as a granulation tool. The influence of processing parameters and formulation variables on the extrudates was evaluated, but the quality of granules was not reported.

In previous chapters (see also Keleb et al., 1999, 2002) we studied twin screw extrusion in combination with an oscillating granulator for the wet granulation of α-lactose monohydrate. This technique was more efficient than high shear granulation and the granules produced had improved properties. However, wet sieving of the material discharged from the twin screw extruder was still required to obtain granules. The aim of this study was to eliminate this wet

sizing step by changing the screw configuration. Some reports indicated that granule quality is influenced by this parameter: Lindberg et al. (1987 and 1988) reported that a low agitation screw profile resulted in a higher yield on granulation and a lower granule porosity than a medium agitation screw profile. Similarly, Lindberg (1988) stated that screw configuration significantly influenced the granule porosity. In addition the process continuity, the maximal capacity and the influence of processing parameters and formulation variables on the granule and tablet properties were evaluated during this research work.

5.2 Materials

α-Lactose monohydrate 200M was used as excipient (DMV, Veghel, The Netherlands) with a particle size distribution of: 60% < 45 µm, 83% < 75 µm, 92% < 100 µm, 98% < 150 µm, 100% < 250 µm (DMV International, 1998). Polyvinylpyrrolidone (PVP, Kollidon® K30) was selected as a binder (BASF, Ludwigshafen, Germany) and hydrochlorothiazide (Ludeco, Brussels, Belgium) as a model drug for poorly water soluble drugs.

5.3 Methods

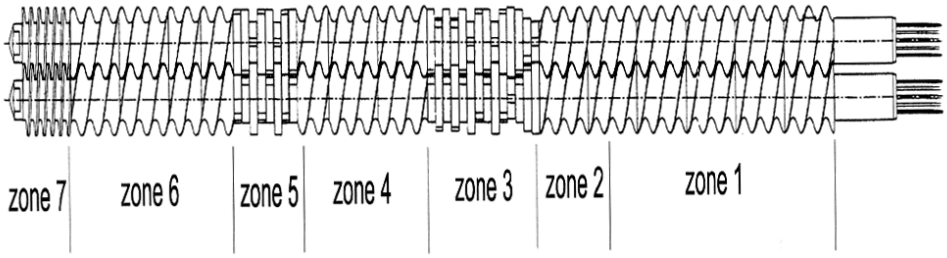
5.3.1 Preparation of granules

The extrusion was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1. During granulation the powder volume in the feed hopper was maintained between 85 and 100% of the feeder capacity. Powder and granulation liquid feed rates were determined prior to each experiment by repeatedly weighing the powder and the liquid amount delivered over a period of 5 min. The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the extruder barrel by means of a peristaltic pump (Watson Marlow, Cornwall, UK). To evaluate the dissolution properties, hydrochlorothiazide (10%) (Ludeco, Brussels, Belgium) was added as a model drug to a formulation without and with 2.5% PVP. Prior to granulation, hydrochlorothiazide was blended with α-lactose monohydrate in a planetary mixer (Kenwood Major, Hampshire, UK) for 15 min at 60 rpm.
The extruder was set at a constant temperature of 25°C. Granules were collected 10 min after the process was started in order to allow the system to equilibrate. The granules were oven-dried at 25°C for 20 h, sieved through a 1400 µm sieve and evaluated for yield, granule

friability and compressibility. Based on preliminary experiments using α-lactose monohydrate and water (as a granulation liquid) a set of reference conditions for the extrusion process was selected: a screw speed of 250 rpm, a total input rate of 5.6 kg/h and a water concentration during granulation of 8.5 and 7.5% (w/w) for formulations without and with 2.5% (w/w) PVP, respectively. All water concentrations were based on the wet granule mass, while PVP and hydrochlorothiazide concentrations were based on dry weight.

The reference conditions were used to optimize the extruder configuration for continuous granulation. In a first approach the die was modified. For these experiments the extruder was equipped with a standard screw profile (Fig. 1a). The initial die configuration studied was a screen (∅1 mm) fixed to the outside of the die block, next the screen was replaced with a 1 mm perforated die plate (2 mm thick) and finally the process was run without the die block.

a.



b.

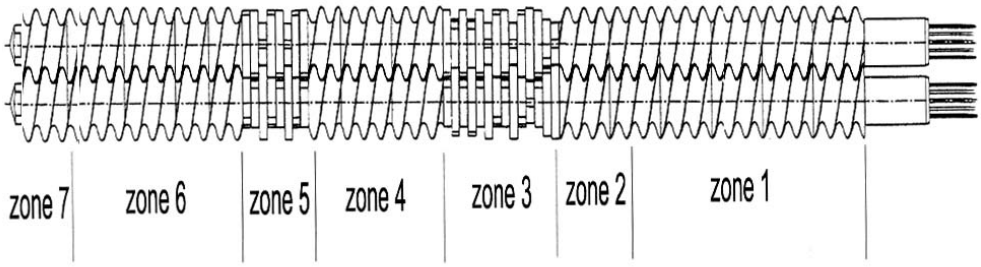


Figure 1: Configuration of the co-rotating screw: feeding zone (1), transition zone (2), mixing zone (3), transport zone (4), mixing zone (5), transport zone (6), feed zone towards the die (7).

(a) Standard screw profile.

(b) Modified screw profile with two mixing zones.

In a second approach, the screw profile was changed. At the end of the screw (zone 7) the discharge screw element was replaced by a conveying screw element (Fig. 1b). Using this modified screw profile, the process was run with and without the die block. The optimal configuration was determined by analyzing the granule yield. Optimization was continued till a granule yield similar to the semi-continuous extrusion/granulation process (Keleb et al., 2002) was achieved. To investigate the efficiency of this continuous granulation process, the granules were evaluated for friability, yield and compressibility. Tablets were evaluated for tensile strength, friability and disintegration. In addition, the between-day reproducibility (n=6) of a formulation without and with PVP and the influence of processing parameters and formulation variables were evaluated.

The maximal capacity of the equipment at optimal configuration was assessed using the maximum screw speed (450 rpm) in combination with a water concentration of 7.5%. The granules obtained at each input rate were evaluated. The continuity of the process for α-lactose monohydrate containing 2.5% PVP was assessed by running the process at reference conditions for 8 h and each hour evaluating the granules and tablets properties.

5.3.2 Compression of tablets

The same method as described in Chapter 3 was used to manufacture the tablets.

5.3.3 Granule evaluation

The characteristics of the granules (particle size, yield, friability and density) were determined using the same methods as described in chapter 3.

5.3.4 Tablet evaluation

The same methods as described in Chapter 3 were used to determine the friability, tensile strength and disintegration time of the tablets.

Dissolution tests were performed on hydrochlorothiazide tablets in 900 ml 0.1N HCl using the paddle method (Vankel, Cary, NC, US). The dissolution medium was maintained at 37 ± 0.5°C, while the rotation speed was set at 100 rpm (USP XXIII). Samples (5 ml) were withdrawn after 5, 10, 15, 20, 25, 30, 45 and 60 min and concentrations were spectrophotometrically determined at 272 nm (Lambda 12 Perkin Elmer, Norwalk, US).

5.4 Statistical analysis

The influence of water concentration, screw speed and total input rate on the granule and tablet properties was determined using one-way ANOVA. Properties of granules and tablets prepared by continuous twin screw granulation over a period of 8 h were analyzed using one-way ANOVA. For further comparison a multiple comparison among pairs of means was performed using a Scheffé test with $p < 0.05$ as a significance level. The influence of PVP concentration was evaluated only within the optimal range of water concentration. The data were tested for normal distribution with a Kolmogorov-Smirnov test and the homogeneity of the variances was tested with a Levene's test. Tablet friability and granule yield could not be statistically analyzed as only one measurement was performed per factor level. Statistical analysis was carried out using the software package SPSS version 11.0.

5.5 Results and discussion

5.5.1 Influence of extruder set-up

Previously Keleb et al. (2002) (see also chapter 3) described extrusion of α-lactose monohydrate 200M using a twin screw extruder equipped with screws having a standard screw profile and with a die block (2.2 by 1.0 cm die aperture), yielding extrudates ranging from small flakes to large extrudates depending on the water concentration used. Modification of the process parameters did not allow to obtain granules and an additional wet sizing step was always required. Although Lindberg et al. (1988 and 1987) and Kleinebudde and Lindner (1993) reported on wet granulation using a twin screw extruder equipped with a perforated die, our attempts to granulate α-lactose monohydrate using a twin screw extruder equipped with a 1-mm screen failed due to the high power consumption, the high barrel temperature, screen distortion and/or screw blocking. Similar problems were observed when a perforated die plate was used instead of the screen. This failure could be explained by the low water concentration used in our study and the different material properties. Increasing the water concentration during extrusion avoided these problems, but this resulted in overwetted sticky extrudates and not in granules. As the densification of the material before the die seemed to be too high the twin screw extruder was used without the die block in combination with the standard screw profile (Fig. 1a) to avoid extrusion of the material. Using this configuration processing of α-lactose monohydrate at optimum water concentration resulted

in a granulation yield of 16% and 22% for α-lactose monohydrate 200M without and with 2.5% PVP, respectively. Using the equipment without die block reduced the resistance to the material flow in the barrel and thereby the load on the machine. This configuration also allowed a higher total input rate, resulting in a higher granulation capacity.

The screw profile was modified as the discharge screw element was replaced by a conveying screw element (Fig. 1b). The effect of this screw modification was evaluated at reference conditions using the extruder with die block, and allowed to produce granules, but the yield was still very low (5.4 and 3% for α-lactose monohydrate formulations without and with PVP, respectively).

However, removing the die block and using the modified screw profile resulted in a yield of 54 and 43% for α-lactose monohydrate without and with PVP, respectively (Table 1), while no lumps (> 2 mm) were produced. This unexpected increase of the yield was mainly due to a decrease in large agglomerates. Removal of the die block and replacement of the discharge screw element by a conveying screw element dramatically reduced the pressure built up at the end of the barrel and avoided compression of the granules. This configuration resulted in a comparable yield with the extrusion/granulation technique combined with wet sieving (60%) as reported by Keleb et al. (2002). In addition the particle fraction smaller than 125 μm ($F_{<125\ \mu m}$) was below 3 and 9 for formulations with and without PVP, respectively. As the twin screw extruder with this optimal configuration yielded granules while no extrusion took place the process will be further referred to as twin screw granulation. In a second part of the study, the granulation process using this twin screw granulation technique was further investigated.

Table 1 shows the properties of granules and tablets obtained after twin screw granulation at reference conditions. α-Lactose monohydrate granules without and with 2.5% PVP had a granule friability below 21%, a yield above 43% and a compressibility below 13%.

α-Lactose monohydrate tablets without PVP had a tensile strength of 0.80 MPa, a friability of 1.6% and a disintegration time of 159 s. Addition of PVP improved the friability (0.8%) and the tensile strength (1.21 MPa) and increased the disintegration time to 509 s. The quality of α-lactose monohydrate granules and tablets produced by twin screw granulation indicated the efficacy of this process. The between day reproducibility showed that the process is reproducible with respect to the granule and tablet properties (Table 1).

Table 1: Between day reproducibility of the twin screw granulation of α-lactose monohydrate. Granules were produced (n=6) at reference conditions without and with 2.5% PVP.

	Granule properties						Tablet properties		
PVP	Friability	Yield	Particle size distribution			Compressibility	Tensile strength	Friability	Disintegration
(%)	(%)	(%)	<250µm	250-1000µm	>1000µm	(%)	(MPa)	(%)	(s)
0	14	55	12	68	20	10	0.64	1.7	173
	23	53	25	62	13	10	0.87	1.7	157
	24	53	24	65	11	14	0.77	1.7	155
	21	58	17	69	14	14	0.81	1.5	169
	21	55	10	66	24	13	0.75	1.6	159
	22	47	29	54	17	13	0.74	1.4	140
avg	21	54	20	64	17	12	0.80	1.6	159
sd	3.5	3.8	7.7	5.5	4.8	1.8	0.08	0.1	11.6
2.5	12	44	12	62	26	13	1.29	0.7	497
	17	47	12	64	24	15	1.23	0.9	494
	10	46	10	65	25	13	1.21	0.8	506
	12	41	6	62	31	13	1.18	0.8	474
	13	42	11	63	27	13	1.23	0.8	520
	10	38	4	58	38	13	1.14	0.7	562
avg	12	43	9	62	29	13	1.21	0.8	509
sd	2.6	3.4	3.4	2.4	5.2	0.8	0.05	0.1	30

5.5.2 Influence of formulation

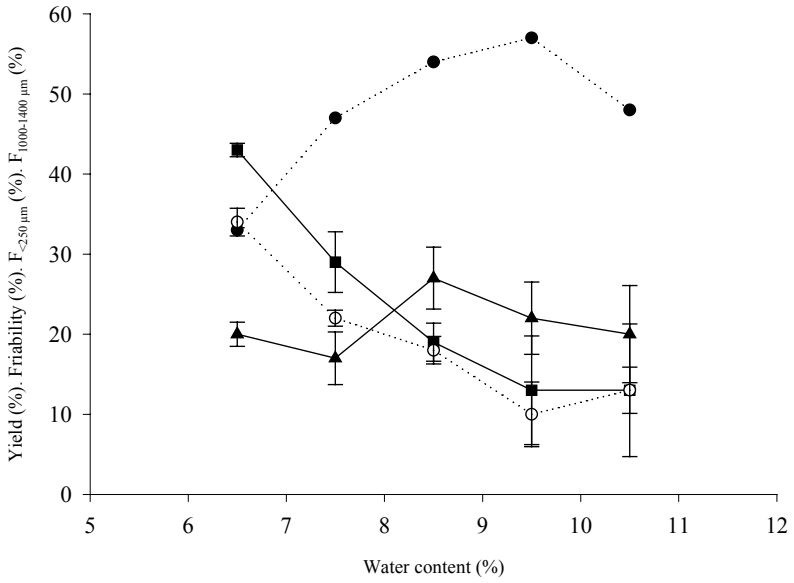
5.5.2.1 Influence of water concentration

The influence of water concentration during granulation on the granule properties is shown in Fig. 2. The water concentration had a crucial influence on the granulation process as well as on the granule yield ($F_{250\text{-}1000\ \mu m}$) confirming earlier findings (Kleinebudde and Lindner, 1993; Keleb et al., 2002). Granulation was only feasible within a specific water concentration range. The determination of the optimum water concentration was based on the yield on granulation. The optimum water concentration is lower when PVP was added and was 8.5 and 7.5% for the granulation of α-lactose monohydrate without and with PVP, respectively. These water concentrations are lower than those used for conventional wet granulation techniques, such as fluid bed or high shear. Moreover, experiments showed that this water concentration can be further reduced by increasing the PVP concentration to 5%. Granulation at a low water concentration not only allowed to reduce the drying time, but could also allow to perform drying in a continuous way.

At optimum water concentration a yield of about 50% was obtained and no lumps (> 2 mm) were formed. Decreasing the water concentration resulted in a higher $F_{<250\mu m}$ mainly due to insufficient granulation, while increasing the water concentration above the optimum level resulted in a gradual increase of the granule fraction $F_{>\ 1400\mu m}$, probably due to overwetting of the agglomerates. However, the $F_{<125\ \mu m}$ was below 5 and 11% for all formulations with and without PVP, respectively. At considerably higher water concentrations the granulation process yielded large flakes instead of granules. This observation stresses the need for an accurate and constant feeding of the binding liquid as well as of the powder during the granulation process. Variations in the feeding rate would result in variable water concentrations and hence have an important impact on the granulation process as well as on the granule yield.

Table 2 shows the properties of tablets obtained from granules produced at different water concentrations. Analysis of these results revealed that the water concentration did not have significant influence on the tablet properties. For α-lactose monohydrate tablets without PVP the tensile strength ranged between 0.49 and 0.75 MPa, the friability was above 1.41% and the disintegration time ranged between 124 and 200 s.

a.



b.

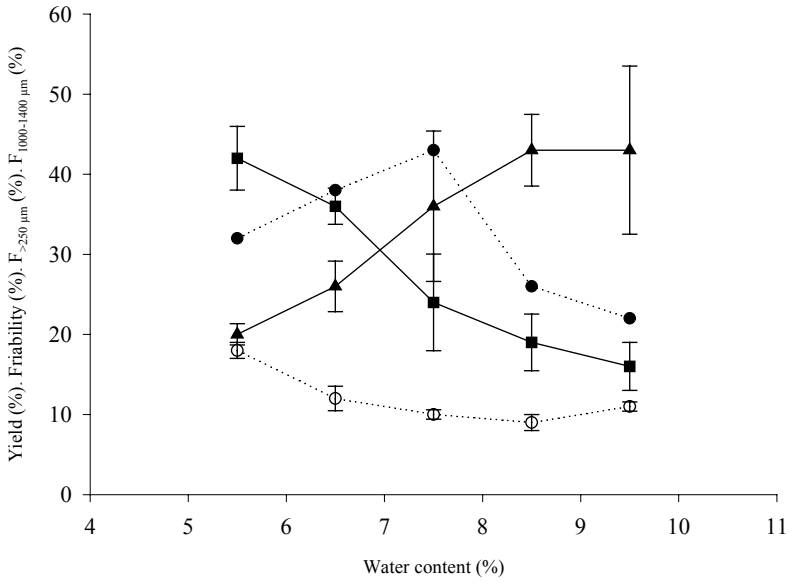


Figure 2: Influence of water concentration during granulation on the properties of α-lactose monohydrate granules granulated at a screw speed of 250 rpm and a total input rate of 5.6 kg.h^{-1}. (●) granule yield, (▲) granule fraction (1000-1400 µm), (○) granule friability, (■) granule fraction < 250 µm. (a) formulated without PVP. (b) formulated with 2.5% PVP.

Table 2: The influence of process parameters and formulation variables on the properties of tablets made from granules produced using twin screw granulation.

Parameters				Tablet properties		
Screw speed	**PVP**	**Total input rate**	**Water**	**Tensile strength**	**Friability**	**Disintegration**
(rpm)	***(%)***	***(kg/h)***	***(%)***	***(MPa)***	***(%)***	***(s)***
Influence of water concentration						
250	0	5.6	6.5	0.75	2.2	124
			7.5	0.74	1.4	140
			8.5	0.69	1.5	144
			9.5	0.49	1.6	165
			10.5	0.71	1.4	200
250	2.5	5.6	5.5	1.02	0.4	459
			6.5	1.02	0.6	493
			7.5	1.09	0.7	510
			8.5	1.27	0.7	523
			9.5	1.17	0.7	575
Influence of PVP concentration						
250	0	5.6	7.5	0.76	1.6	159
250	1.25	5.6	7.5	1.22	0.9	352
250	2.5	5.6	7.5	1.21	0.8	509
Influence of screw speed						
200	0	5.6	8.5	0.68	1.6	219
250				0.66	1.6	204
300				0.66	1.6	175
350				0.67	1.5	176
400				0.68	1.7	185
450				0.70	1.5	204
200	2.5	5.6	7.5	1.22	0.7	545
250				1.18	0.6	543
300				1.10	0.6	557
350				0.94	0.7	530
400				1.25	0.7	553
450				1.22	0.6	535
Influence of total input rate						
250	0	5.6	8.5	0.77	1.9	205
		6.5		0.78	1.8	192
		7.5		0.75	1.4	179
		8.5		0.70	1.4	173
		9.5		0.71	1.1	157
250	2.5	5.6	7.5	1.14	0.7	562
		6.5		1.04	0.5	523
		7.5		1.11	0.5	576
		8.5		1.09	0.8	544
		9.5		1.02	0.5	525
Maximum capacity						
450	2.5	5.6	7.5	1.22	0.6	535
		10.5		1.10	0.9	496
		12.5		1.12	0.6	468
		16.5		1.15	0.9	502
		18.5		1.11	0.5	501

For α-lactose monohydrate tablets with 2.5% PVP the tensile strength ranged between 1.02 and 1.17 MPa, the friability between 0.39 and 0.68% and the disintegration time between 459 and 575 s. At all water concentrations the tablets with PVP had a significantly higher tensile strength and disintegration time than those without PVP.

5.5.2.2 Influence of PVP concentration

The addition of 2.5% PVP resulted in a lower $F_{<250\ \mu m}$, a significantly lower granule friability and a higher $F_{>1400\ \mu m}$. The shift in granule size distribution towards large particles is mainly due to good binding properties of PVP (Wikberg and Alderborn, 1992, Wan et al., 1996). Reducing the PVP concentration to 1.25% PVP resulted in a similar granule friability and $F_{<250\ \mu m}$ as those obtained for 2.5% PVP, but it slightly increased the yield and decreased $F_{>1400\ \mu m}$ as shown in Fig. 3. The $F_{<125\ \mu m}$ was below 5 and 11% for formulations with and without PVP, respectively.

The addition of PVP (1.25 or 2.5%) significantly increased tablet tensile strength, decreased tablet friability to below 1% and significantly increased tablet disintegration time, however it remained below 10 min (Table 2). Similar properties were obtained for α-lactose monohydrate tablets containing 1.25 and 2.5% PVP. These results indicated that 1.25% PVP would be sufficient for the granulation of α-lactose monohydrate using twin screw granulation.

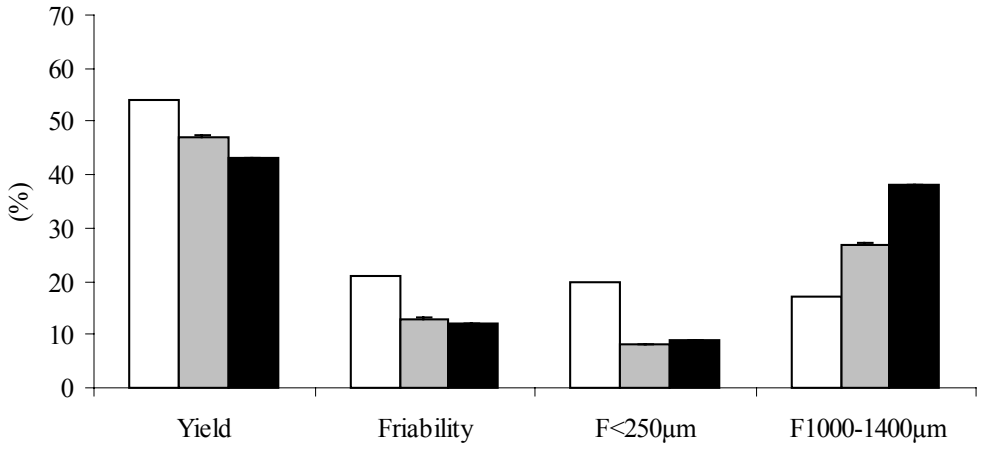


Figure 3: Influence of PVP concentration on the properties of α-lactose monohydrate granules containing 0 (□), 1.25 (▒) and 2.5% PVP (■).

5.5.3 Influence of processing parameters

5.5.3.1 Influence of the screw speed

Screw speed had a significant effect on some properties of granules containing PVP (Fig. 4), while it did not affect the properties of pure α-lactose monohydrate 200M granules. Increasing the screw speed from 200 to 450 rpm at a constant total input rate had no significant influence on the granule friability, while it resulted in a decrease of the granulation yield from 48% to 32% and in an increase of the fraction $F_{> 1400\mu m}$ from 31 to 50%. This effect was probably due to incomplete filling of the granulator barrel as the screw speed increased, creating less friction and collisions between agglomerates thus allowing the granules to grow. The effect was only observed when PVP was added, indicating the strong adhesion and binding properties of PVP. The compressibility was always below 15%, indicating the good flow properties of the granules. Table 2 shows that the screw speed had no significant influence on the tablet properties.

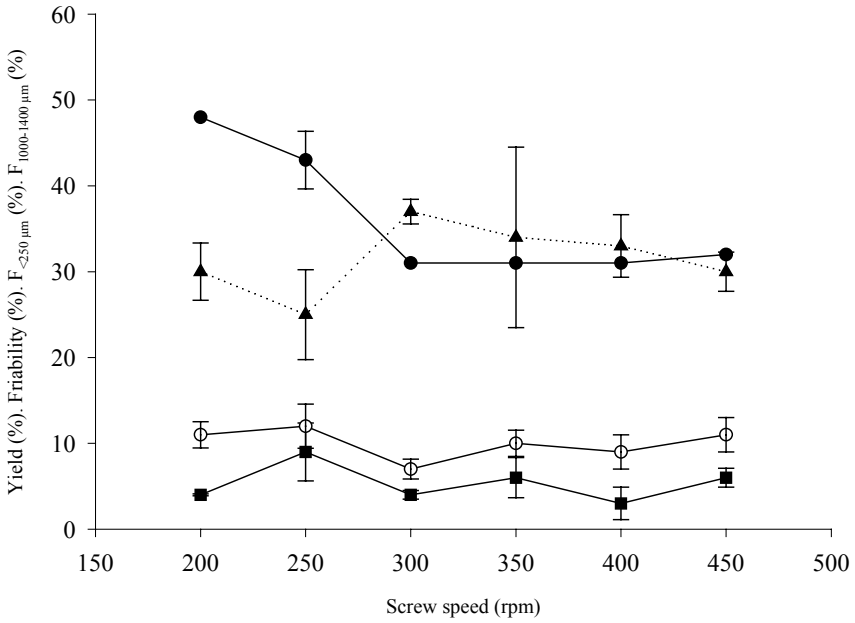


Figure 4: Influence of screw speed on the granule properties of α-lactose monohydrate granules with PVP granulated at a water concentration of 7.5% and a total input rate of 5.6 $kg.h^{-1}$ (●) granule yield, (▲) $F_{1000\text{-}1400\ \mu m}$, (○) granule friability, (■) $F_{< 250\ \mu m}$.

5.5.3.2 Influence of total input rate

The influence of total input rate (i.e. powder + liquid feed rate) on the granule properties is shown in Fig. 5. It is clear that increasing the total input rate had no influence on the granule properties except on the granulation yield, which increased as the total input rate increased. As for the effect of screw speed, this can be explained by the different degree of filling of the granulator barrel. At a higher total input rate, the filling degree of the barrel was higher, causing an increase in friction and collisions between the agglomerates and resulting in more agglomerate breakdown and hence increasing the yield. The compressibility was always below 15%, indicating the good flow properties of the granules.

Table 2 shows that total input rate had no significant influence on the tablet properties.

5.5.4 Maximum capacity

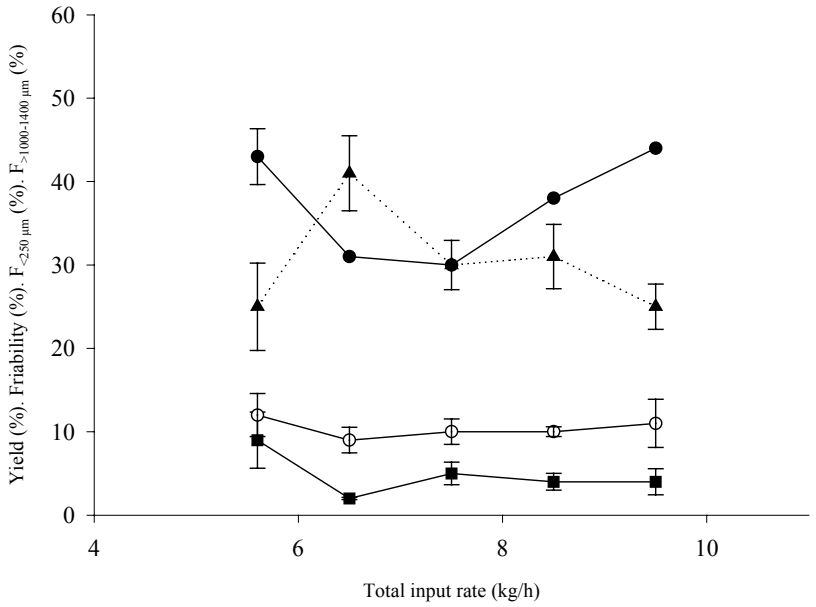
The capacity of the twin screw granulator was also determined for α-lactose monohydrate 200M with 2.5% PVP. As shown in Fig. 5b and Table 2, the total input rate could be increased from 5.5 up to 18.5 kg/h with limited influence on the granule and tablet properties.

Beyond 18.5 kg/h the powder accumulated at the inlet of the granulator barrel. As the power consumption measured at this high input rate remained at 30% (a value similar to that recorded at lower total input rates) this is an indication that the machine is not fully loaded at 18.5 kg/h and that the capacity of the granulation process can possibly be increased by modifying the powder inlet system of the granulator barrel.

5.5.5 Process continuity

The continuity of twin screw granulation was evaluated over a period of 8 h. No problems were noticed during the 8 h of granulation. Moreover, the power consumption always ranged between 26 and 28%, and the barrel temperature between 56 and 66°C. The granule and tablet properties are shown in Fig. 6a and b, respectively. Analysis of the results revealed no significant differences in granule and tablet properties over the entire granulation period.

a.



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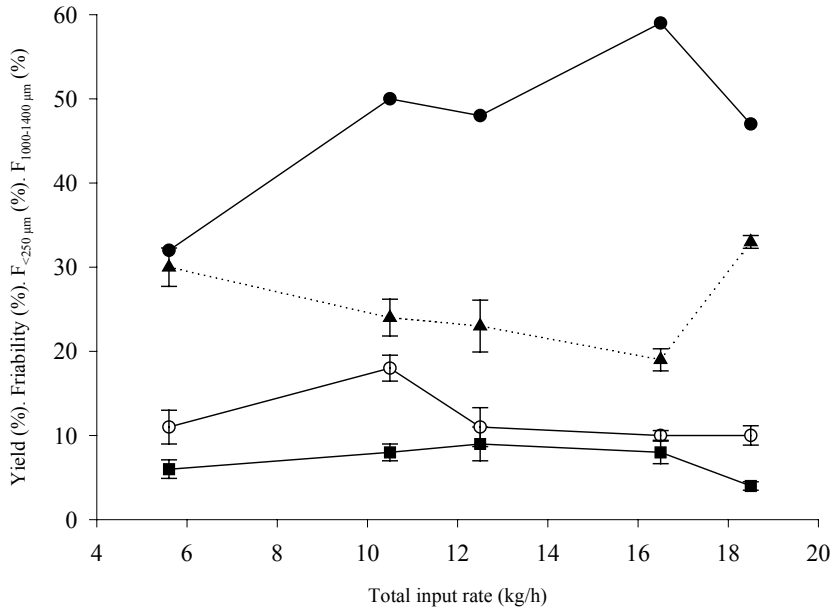

Figure 5: Influence of total input rate on the properties of α-lactose monohydrate granules with PVP granulated at a water concentration of 7.5%. Screw speed: (a) 250 rpm, (b) 450 rpm. (●) granule yield, (▲) $F_{1000\text{-}14000\mu m}$, (○) granule friability (■), $F_{< 250\mu m}$

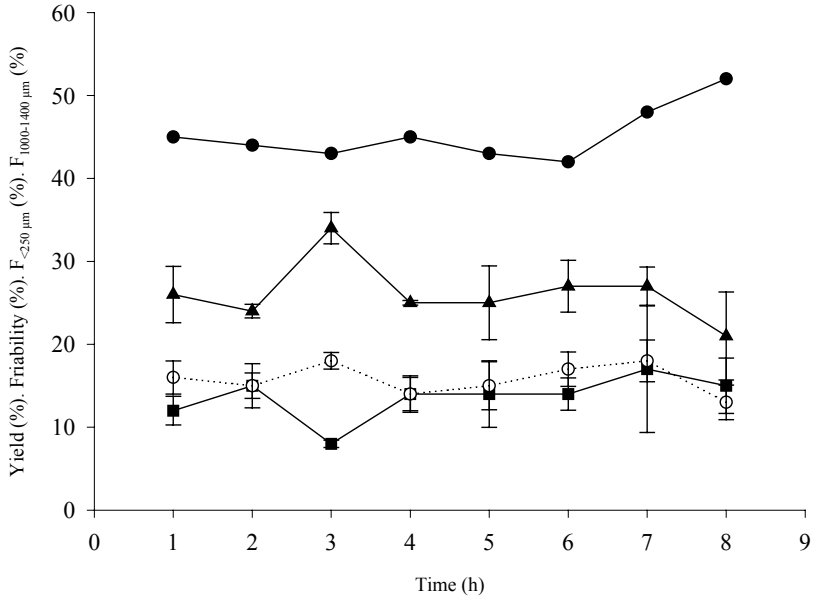

Figure 6a: Properties of α-lactose monohydrate granules with PVP, produced by continuous twin screw granulation over a period of 8 h, granulated at a water concentration of 5.5%, screw speed of 250 rpm and a total input rate of 5.6 kg.h^{-1}. (●) granule yield, (▲) $F_{1000\text{-}1400\ \mu m}$, (○) granule friability, (■) $F_{< 250\ \mu m}$.

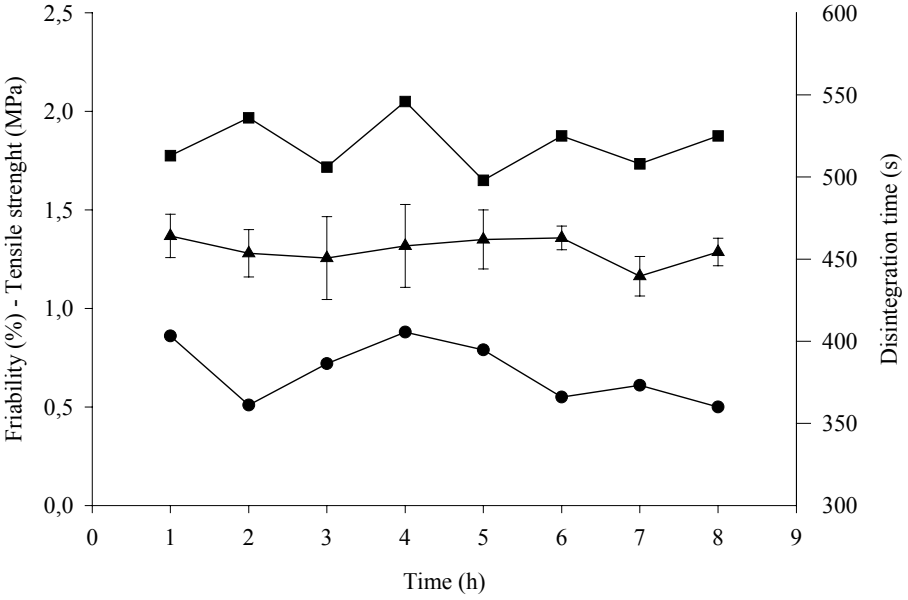

Figure 6b: Properties of tablets made from α-lactose monohydrate granules with PVP produced by continuous twin screw granulation over a period of 8 h. (●) friability, (▲) tensile strength, (■) disintegration time.

From this it can be concluded that the twin screw granulator is suitable for continuous wet granulation of α-lactose monohydrate 200M.

5.6 Conclusion

The twin screw granulation process optimized in this study allowed continuous and efficient wet granulation of α-lactose monohydrate 200M. Acceptable tablet properties were obtained only when PVP was added as a binder during granulation.

Optimization of water concentration and controlling the water and powder feeding rate during granulation were essential for the process performance and continuity. Increasing the screw loading improved the granulation performance, especially for formulations containing PVP.

The study showed that twin screw granulation is a promising continuous wet granulation technology.

5.7 References

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6 Twin screw granulation as a continuous wet granulation technique: influence of filler properties and application to highly dosed drug formulations

6.1 Introduction

In the pharmaceutical industry formulations intended for tablet production are often granulated prior to tabletting. The granule properties depend on the granulation process, and are determined by the binder distribution as well as by the granulation mechanism. Additionally the chemical properties of the materials to be granulated and the variability of their physical properties (particle size and morphology) will affect processing and determine the granule and tablet properties.

In the pharmaceutical industry granule production is mainly based on a batch type procedure, but recently a growing interest for continuous production (especially for high volume products) is seen. Switching towards continuous production requires a robust process that is able to compensate for raw material variability, has stable steady state conditions and requires minimal scale-up.

Continuous twin screw granulation is a continuous wet granulation technique derived from extrusion granulation (Chapter 3) (Keleb et al., 2002), which allows granulation without wet sieving (Chapter 5) (Keleb et al., 2004). Lactose is a widely used excipient in the production of granules and tablets and exists in different grades having different physical properties. The objective of the present study was to examine the influence of lactose with different particle size and morphology on the properties of granules and tablets obtained by continuous twin screw granulation. Finally the continuous twin screw granulation process was applied to two highly dosed drug formulations containing paracetamol and cimetidine.

6.2 Materials

The same materials were used as described in Chapter 4.

6.3 Methods

6.3.1 Continuous twin screw granulation

Granulation was performed on a twin screw granulator described by Keleb et al. (2004). Granulation of the lactose grades and of formulations containing paracetamol and cimetidine was performed at 25°C barrel temperature, 250 rpm screw speed, 5.6 $kg.h^{-1}$ total input rate (powder and liquid feed rate) and 8.5 and 7.5% water concentration for formulations without and with 2.5% (w/w) PVP, respectively. The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the granulator barrel using a peristaltic pump (Watson Marlow, Cornwall, UK). Granules were collected 10 min after the process was started in order to allow the system to equilibrate and oven-dried at 25°C for 20 h. If required, paracetamol or cimetidine were blended before granulation with α-lactose monohydrate for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). All water concentrations were based on wet mass, while PVP, cimetidine and paracetamol concentrations were based on dry weight. The granulation process was evaluated by monitoring power consumption and barrel temperature. If the power consumption exceeded 80% of the maximum capacity the process was stopped in order to avoid machine damage.

6.3.2 Compression of tablets

The same method as described in Chapter 3 was used to manufacture the tablets.

6.3.3 Granule evaluation

The same methods as described in Chapter 3 were used to determine the yield of the process and the particle size, friability and density (bulk and tapped) of the granules.

6.3.4 Tablet evaluation

Tablet friability, tensile strength and disintegration time were determined as described in Chapter 3. To determine tablet porosity and in-vitro dissolution the methods described in Chapter 4 were used.

6.4 Statistical analysis

The influence of lactose particle size and morphology on granule friability, tablet tensile strength and disintegration time was determined using one-way ANOVA. For further comparison of the influence of these parameters on the granule and tablet properties a multiple comparison among pairs of means was performed using the Scheffé test with $P < 0.05$ as a significance level. The data were first tested for normality with a Kolmogorov-Smirnov test and for the homogeneity of variances with a Levene's test. Statistical analysis was performed using the computer software SPSS version 11.0.

6.5 Results and discussion

6.5.1 Granulation of lactose

As a constant powder feed rate is a prerequisite for a reproducible granule quality, a double screw feed system was used to ensure a constant powder feed rate during continuous granulation. However, only α-lactose monohydrate 200M was delivered at a constant rate during granulation. With the other lactose grades several problems were encountered: a gradual decrease in feed rate and difficulties with the screw rotation (or even blocking of the screw movement) were observed for α-lactose monohydrate 100M, 90M and anhydrous β-lactose. α-Lactose monohydrate 450M tended to adhere to the hopper surface, mainly due to the cohesiveness of its particles. This did not hamper the accuracy of the feed rate during short time processing. However, these observations emphasized the need to design feeding systems allowing a constant and reproducible feeding of a broad range of materials during long term processing.

The water concentration was optimised for α-lactose monohydrate 200M (Chapter 5) and this water concentration was used for the granulation of all lactose grades. The water concentration used during continuous twin screw granulation resulted in a yield between 43 and 60% for all grades of lactose, independent of the use of PVP as a binder. Comparison of these results to those obtained by extrusion/granulation and high shear granulation (Chapter 4) indicate that continuous twin screw granulation possibly requires less optimisation when applied to materials with different physical characteristics.

During continuous twin screw granulation of different grades of α-lactose monohydrate the barrel temperature and power consumption were decreased as lactose particle size increased

mainly due to improved lubrication (Table 1). However, a higher barrel temperature and power consumption were observed for anhydrous β-lactose than for the α-lactose monohydrate grades, mainly due to the higher friction during granulation. Anhydrous β-lactose consists of granular particles with irregular shape and high strength resulting in a higher friction.

Table 1: Process parameters during continuous twin screw granulation of different lactose grades.

PVP *(%)*	**Power consumption** *(%)*	**Barrel temperature** *(°C)*
α-Lactose monohydrate 450M		
0	29	44
2.5	27	43
α-Lactose monohydrate 200M		
0	24	42
2.5	25	44
α-Lactose monohydrate 100M		
0	17	34
2.5	15	30
α-Lactose monohydrate 90M		
0	20	29
2.5	17	28
Anhydrous β-lactose		
0	37	60
2.5	38	57

The properties of the granules manufactured using continuous twin screw granulation are listed in Table 2. These properties were not affected by particle size and particle shape. The granule friability remained below 23% and the compressibility below 15%. The addition of PVP significantly decreased the friability, while no influence on yield was seen. However, during extrusion/granulation and high shear granulation of the different lactose grades particle size and shape influenced the granule properties (Chapter 4), which indicated that continuous twin screw granulation is more robust than extrusion/granulation and high shear granulation.

Table 2: Granule and tablet properties of different lactose grades prepared by continuous twin screw granulation.

PARAMETERS			GRANULE PROPERTIES					TABLET PROPERTIES			
Lactose type	**PVP** *(%)*	**Water** *(%)*	**Friability** *(%)*	**Yield** *(%)*	**Particle size distribution** *<250 µm*	*250-1000 µm*	*>1000 µm*	**Compressibility** *(%)*	**Tensile strength** *(MPa)*	**Friability** *(%)*	**Disintegration** *(s)*
α-Lactose monohydrate 90M											
	0	8.5	20	48	25	57	19	13	0.75	1.4	159
	2.5	7.5	9	49	16	64	20	14	1.03	0.8	566
α-Lactose monohydrate 100M											
	0	8.5	22	60	4	72	24	13	0.50	2.1	104
	2.5	7.5	15	49	3	74	23	13	0.80	0.9	583
α-Lactose monohydrate 200M											
	0	8.5	21	54	20	64	17	12	0.76	1.6	159
	2.5	7.5	12	43	9	62	29	13	1.21	0.8	509
α-Lactose monohydrate 450M											
	0	8.5	23	55	21	63	16	14	1.00	1.6	120
	2.5	7.5	14	49	15	62	23	13	1.44	0.9	490
Anhydrous β-lactose											
	0	8.5	9	57	5	74	22	12	0.91	1.1	319
	2.5	7.5	10	49	6	70	24	14	1.45	0.7	368

Table 2 also shows the properties of tablets formulated with granules produced using continuous twin screw granulation. In all cases the addition of PVP was required to decrease the tablet friability below 1%. However, the addition of PVP increased the disintegration time of the tablets.

6.5.2 Continuous twin screw granulation of paracetamol

Paracetamol formulations without and with 2.5% PVP were easily processed. The barrel temperature was 44 - 45°C and the power consumption around 30%. The granules obtained were free of lumps. Granulation without PVP resulted in an unacceptable granule friability of 91% and a yield of 44%. Increasing the water concentration to 10.5% did not improve the friability nor the yield. The improvement of friability after PVP addition can be attributed to the PVP interaction with paracetamol (formation of hydrogen bonds) as reported by Garkani (1996). The compressibility ranged between 12 and 14%, indicating good flow properties.

Continuous twin screw granulation of paracetamol resulted in a higher granule yield and a lower friability than extrusion/granulation and high shear granulation (Chapter 4), which indicated that continuous twin screw granulation is more efficient for the granulation of paracetamol.

Paracetamol granules without PVP prepared using continuous twin screw granulation yielded weak tablets without capping or lamination, in contrast to the tablets produced using paracetamol granules prepared by extrusion/granulation (Chapter 4). For paracetamol formulations with 2.5% PVP as a binder, continuous twin screw granulation at the optimal water concentration allowed to obtain tablets with friability below 1%, while extrusion/granulation and high shear granulation failed in providing granules that allowed to manufacture tablets of good quality (Keleb et al., 2004). These results again indicated that continuous twin screw granulation is more efficient than extrusion/granulation and high shear granulation.

Fig. 1 shows the dissolution profiles of tablets made from paracetamol/PVP granules. In order to comply with the pharmacopoeial requirements the addition of 5% crospovidone was required.

Table 3: Granule and tablet properties of formulations containing paracetamol and cimetidine prepared by continuous twin screw granulation.

Processing variables			**Granule properties**						**Tablet properties**		
Drug	**Water**	**PVP**	**Friability**	**Yield**	**Particle size analysis**			**Compressiblilty**	**Tensile strength**	**Friability**	**Disintegration**
(%)	***(%)***	***(%)***	***(%)***	***(%)***	***< 250µm***	***250-1000µm***	***>1000µm***	***(%)***	***(MPa)***	***(%)***	***(s)***
Paracetamol											
100	8.5	0	91	44	43	47	11	12		Weak tablets	
100	10.5		82	50	32	53	16	13		Weak tablets	
97.5	7.5	2.5	27	50	13	67	20	14	1.98	0.99	3735
92.5*	10.5		27	72	10	81	9	14	0.77	1.28	30
Cimetidine											
100	8.5	0	27	51	28	61	11	15	1.41	0.54	> 3600
97.5	7.5	2.5	16	46	17	67	15	14	1.42	0.88	> 3600
95*	17.5	0	80	45	38	51	10	13	1.30	0.81	35
92.5*	14.5	2.5	27	42	19	57	24	15	1.93	0.72	148

* Containing 5% crospovidone

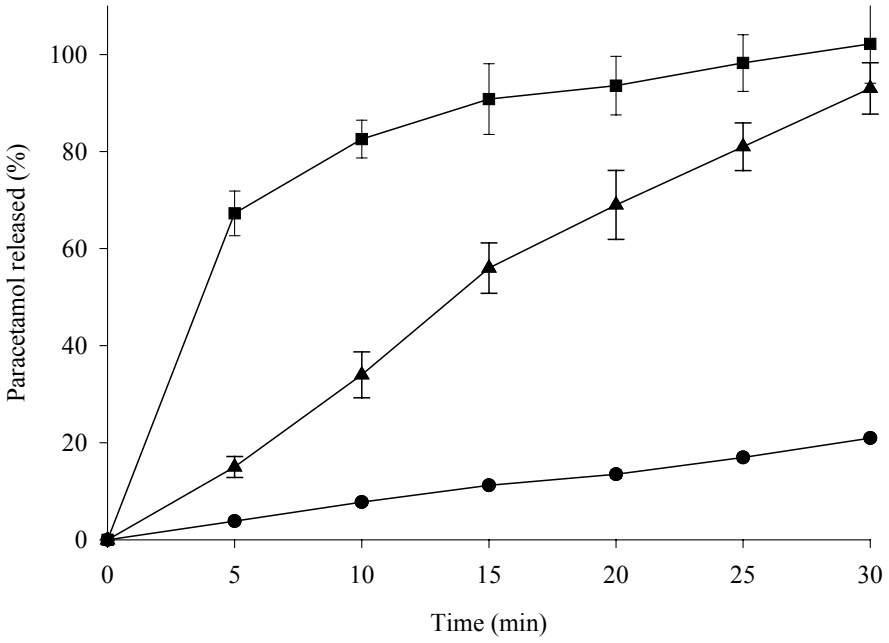

Figure 1: Dissolution profiles of tablets containing 80% paracetamol/17.5% α-lactose monohydrate/2.5% PVP (▲), 97.5% paracetamol/2.5% PVP (●) and 92.5% paracetamol/2.5% PVP/5% crospovidone (■). The tablets were prepared from granules produced by continuous twin screw granulation.

6.5.3 Continuous twin screw granulation of cimetidine

Cimetidine was easily granulated by continuous twin screw granulation at reference water concentration without as well as with binder. The granulation process was associated with a barrel temperature of 54-56°C and a power consumption of 41-44%. However, increasing the water concentration to 14.5% reduced the barrel temperature below 42°C and the power consumption below 21%. Continuous twin screw granulation of cimetidine without PVP at reference conditions resulted in a granule yield of 51% and a granule friability of 27%. Addition of 2.5% PVP reduced the friability to 16% with a yield of 46%.

Granulation of cimetidine using continuous twin screw granulation was easier and resulted in improved granule properties compared to extrusion/granulation and high shear granulation (Keleb et al., 2004). These results indicated that continuous twin screw granulation is more efficient for granulation of cimetidine.

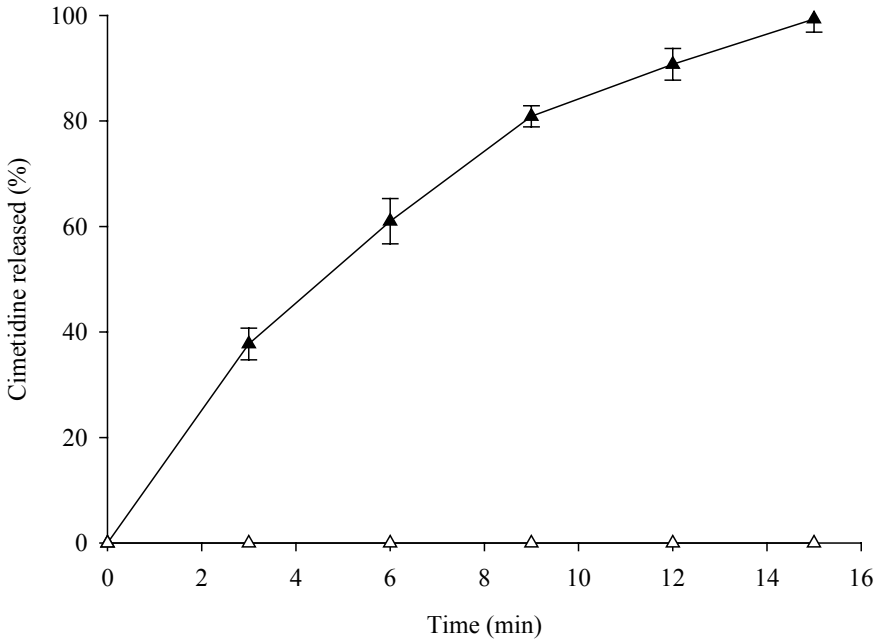

Figure 2: Dissolution profiles of cimetidine tablets (containing 2.5% PVP) without (Δ) and with (▲) 5% crospovidone. The tablets were prepared from granules produced by continuous twin screw granulation.

Table 3 shows the properties of cimetidine tablets compressed from granules produced by continuous twin screw granulation. A friability below 1% and a tensile strength below 1.4 MPa were recorded. However, the disintegration time was over 1h and the dissolution failed to meet the USP requirements. Again the addition of 5% crospovidone reduced the disintegration time to below 154 s with a release of 60% within 15 min.

6.6 Conclusion

This study showed that during granulation of different lactose grades, the particle size and morphology only had a limited influence on the continuous twin screw granulation process. Continuous twin screw granulation of highly dosed drugs (paracetamol and cimetidine) was efficient, resulting in a good yield and a low friability. However, optimisation of the water and PVP concentration was required to allow smooth granulation as well as to obtain acceptable granule and tablet properties. From these results it was concluded that continuous twin screw granulation is an efficient and simple tool for continuous wet granulation.

6.7 References

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Keleb E.I., Vermeire A., Vervaet C., Remon J.P. (2004). Twin screw ganulation as a simple and efficient tool for continuous wet granulation. Int. J. Pharm., **273**, 183-194.

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7 Cold extrusion as a continuous single-step granulation and tabletting process

Published in Eur. J. Pharm. Biopharm., 52 (2001), 359-368

7.1 Introduction

Tablets can be compacted by direct compression or after a granulation step. Direct compression is preferred, but is only possible for a limited number of substances due to problems such as poor powder flow properties, low tablet strength, capping and segregation. Granulation is designed to overcome these problems and usually results in better flowability and compactibility of the powder. In some cases however, problems still exist during the large-scale production of tablets. There is also an increasing interest for continuous operation in the pharmaceutical industry. It is clear that a single-step continuous granulation/tableting process could provide advantages such as reduced investment and labour cost and easier automation of the process.

Several researchers successfully used the hot-melt extrusion technique for the continuous production of, mainly sustained release, tablets (Prapaitrakul et al., 1991; Grunhagen, 1994; Sprockel et al., 1997; Zhang and McGinity 1998; 1999a; 1999b; 2000; Anonymous, 2000), while the potential of cold extrusion as a continuous granulation technique was also reported (Kleinebudde and Lindner, 1993; Gamlen and Eardly, 1986; Lindberg et al., 1987; 1988; Lindberg, 1988). We recently investigated the granulation of α-lactose monohydrate using cold extrusion (Keleb et al., 2002). During these experiments a remarkably high mechanical strength as well as a fast disintegration of extrudates, dried without wet sizing, was noticed. This indicated that a twin-screw extruder equipped with a proper die plate (e.g. having an aperture of 9 mm diameter) could be suited for the production of compact extrudates, which are consequently cut into tablets and dried. Hence, in this study cold extrusion was examined as a single-step granulation/tableting technique for the continuous production of tablets containing components with poor flow and compression properties.

7.2 Materials

α-Lactose monohydrate 200M (DMV, Veghel, The Netherlands) was used as an excipient; water and PVP (Kollidon® K30, BASF, Ludwigshafen, Germany) were used as binders. Hydrochlorothiazide (Ludeco, Brussels, Belgium) was selected as a model drug for poorly water soluble drugs.

7.3 Methods

7.3.1 Preparation of tablets

Extrusion was performed on a laboratory scale co-rotating twin-screw extruder (Model MP 19 TC 25, APV Baker, Newcastle-under-Lyme, UK), having a length-to-diameter ratio of 25/1 and equipped with stainless steel screws with a standard screw profile with two mixing sections. The axial mounted die plate has a cylindrical hole of 9 mm diameter. The α-lactose monohydrate powder and the binding liquid (pure water or aqueous PVP solution) were fed into the first zone of the extruder barrel. The powder was fed on top of the screws using a screw operated feeder, while the liquid was pumped into the barrel by means of a peristaltic pump (Watson Marlow Type 505L, Cornwall, UK). In case where hydrochlorothiazide was present in the formulation it was premixed with α-lactose monohydrate for 15 min in a planetary mixer (Kenwood, Hampshire, UK) at a mixing speed of 60 rpm. All water fractions were calculated based on the wet extruded mass, whereas all PVP and drug concentrations were calculated based on dry tablet weight. The extruder was set at a constant temperature of 25°C. In order to ensure equilibration of the extruder at the test conditions, evaluation of the process feasibility and sampling were started 10 min after the process was started.

Tablets (thickness: 4 mm) were manually cut using surgical blades immediately after extrusion and then oven dried for 20 h at 25°C. After drying, tablets weighing between 245 to 265 mg were selected and stored in a dessicator at 60% RH for 24 h prior to evaluation.

The feasibility of continuous tableting using cold extrusion was evaluated by varying formulation and process parameters. First the optimum water concentration was determined at a screw speed of 250 rpm and a total input rate (powder feed rate +

liquid feed rate) of 5.6 $kg.h^{-1}$ i.e. the standard processing parameters determined during the continuous granulation of α-lactose monohydrate by means of extrusion (Keleb et al., 2002). Before assessing the influence of the process parameters the reproducibility (n=6) of the overall process was determined at the optimum water concentration, using pure water as a binding liquid as well as an aqueous PVP solution. Next, the influence of the process parameters (screw speed and total input rate) on the process and on the tablet quality was determined. Finally, the performance of this technique for the incorporation of drugs was investigated at optimum water concentration and process parameters.

α-Lactose monohydrate tablets (250 mg) were also prepared by direct compression (compression force 10 kN) of the powder on an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm diameter. Prior to compression the powder was blended for 1 min with 0.5% magnesium stearate (< 90μm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland).

7.3.2 Precision of powder and liquid feed rate

Prior to each experiment the powder and liquid feed rates were verified by collecting and weighing (n=3) the powder and the liquid discharged during 5 min.

7.3.3 Process evaluation

7.3.3.1 Power consumption and die pressure

During each experiment power consumption and die pressure were constantly monitored. In order to avoid any damage to the extruder the extrusion process was stopped if the power consumption reached 80% of its maximal value or when a die pressure of 15 bar was recorded.

7.3.3.2 Evaluation of extrudates

The extrudates were visually inspected for any defects (discontinuous extrudate, shark skinning or other deficiencies) and evaluated for their suitability to be cut into tablets (deformation due to cutting, smoothness of the cutting surfaces and the edges).

7.3.4 Tablet evaluation

The methods as described in chapter 3 were used to determine the friability, tensile strength and disintegration time of the tablets. The porosity of the tablets was determined as described in chapter 4.

7.3.4.1 Dissolution test

Dissolution tests of hydrochlorothiazide tablets were performed in 900 ml HCl (0.1N) (37 ± 0.5°C) using dissolution apparatus II (Vankel, Technology Group, Cary, NC, US) at a paddle speed of 100 rpm (USP XXIV). Samples (5 ml) were withdrawn after 5, 10, 15, 20, 25, 30, 45 and 60 min and concentrations were spectrophotometrically determined at 272 nm (Lambda 12 Perkin Elmer, Norwalk, US).

7.4 Statistical analysis

Before any analysis was performed the data were tested for normal distribution with a Kolmogorov-Smirnov test and the homogeneity of variances was tested with a Levene's test. If possible (at least 5 levels of the factor tested and multiple measurements at each point) significant correlations were determined using the Pearson's correlation test ($p<0.05$). For all significant correlations ($p<0.05$) linear regression analysis was performed. In case where the coefficients (slope and intercept) obtained by linear regression are significant ($p<0.05$), these were used to calculate the trend line.

When no correlation test could be performed, the influence of the studied parameter on the tablet properties was determined using a one-way ANOVA ($p<0.05$). To further compare the effects of different parameters a multiple comparison among pairs of means was performed using a Scheffe test with $p<0.05$ as a significance level. Friability results could not be analysed as only one measurement was performed per factor level. For all the statistical analysis the computer program SPSS version 10.0 was used.

7.5 Results and discussion

7.5.1 Precision of powder and liquid feed rate

During determination of the precision of the powder feed rate it was noted that at a constant screw speed, the powder feed rate decreased with decreasing powder level in the feeder. Therefore, the powder level in the hopper was always maintained between 85 and 100% of the total feeder capacity. Under these circumstances reproducible (CV < 2%) powder feed rates were obtained at all feed rates used. For water as well as for the PVP solutions, the variability of the liquid feed rate was below 1% at all pump speeds used.

7.5.2 Determination of optimum water concentration

Table 1 shows the influence of the water concentration during extrusion on the process evaluation parameters. The water fraction of the wet mass had a dramatic influence on the extrusion process and on the cutting of the extrudates.

Table 1: Influence of the water content during extrusion on the process parameters for extrusion of α-lactose monohydrate formulated without PVP and with 2.5% (w/w) PVP at a screw speed of 250 rpm and a total input rate of 5.6 $kg.h^{-1}$.

Formulation		**Process evaluation**		
PVP (%, w/w[1])	Water (%, w/w[2])	Power consumption (%)	Die pressure (bar)	Remarks
0	9.5	-	-	Extrusion not possible, mass too dry
	10.5	29	3	
	11.5	24*	1*	
	12.5	27	2	
	13.5	20	0	Deformation of tablets during cutting
	14.5	17	0	Deformation of tablets during cutting
2.5	7.5	44	7	Extrudate very dry, difficult to be
	8.5	28	7	Extrudate very dry, difficult to be
	9.5	25*	3*	
	10.5	22	1	
	11.5	17	0	Deformation of tablets during cutting
	12.5	19	0	Deformation of tablets during cutting

[1] Based on dry tablet weight ,[2] Based on wet extruded mass, * Average of 6 batches

At standard process parameters, production of α-lactose monohydrate tablets with acceptable shape was feasible only at a water concentration between 10.5 to 12.5 % (w/w) and between 9.5 to 10.5 % (w/w) for formulations without and with PVP, respectively. The lower water concentration required for continuous processing of formulations with PVP can be attributed to the lubricating effect of PVP. Within the respective optimum water concentration the extrudates had a smooth surface, could be cut without causing any deformation and the resulting tablets exhibited smooth surfaces and edges (Fig. 1). Higher water concentration resulted in poorly shaped tablets due to extensive deformation during cutting, while at lower water concentration continuous processing was impossible as within 5 min the power consumption and the die pressure exceeded their maximum set limit. Within the range of water concentration which allowed continuous extrusion, the power consumption varied between 20 and 30% of its maximal value and the die pressure did not exceed 10 bar.

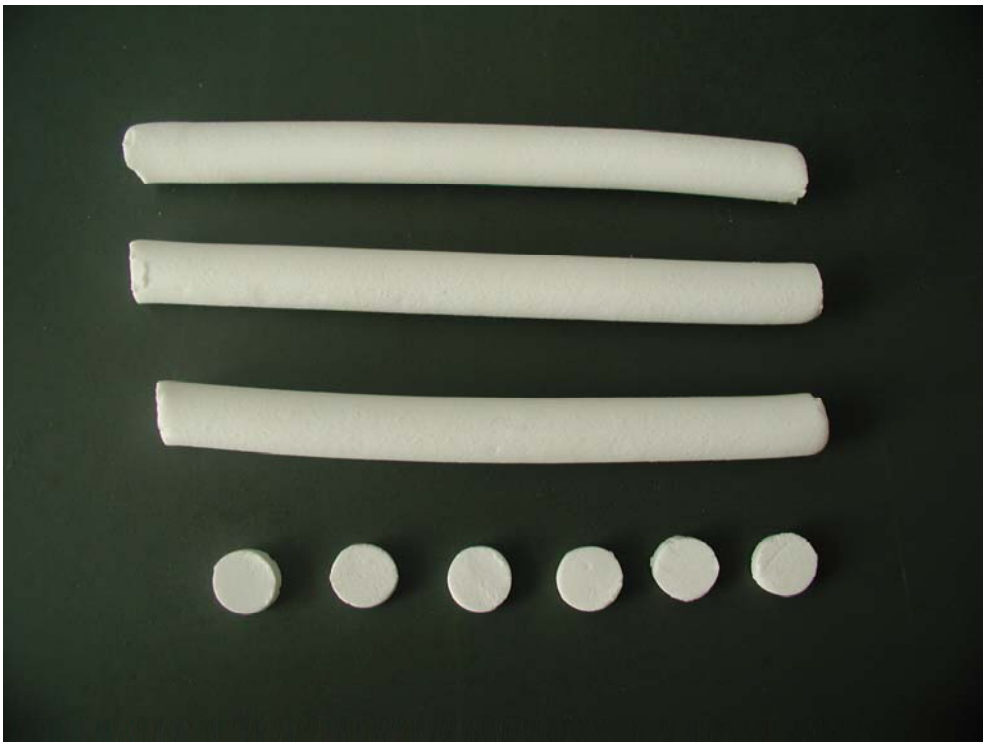


Figure 1: Extrudates and tablets produced by cold extrusion of α-lactose monohydrate formulated without PVP at a screw speed of 250 rpm, a total input rate of 5.6 $kg.h^{-1}$ and a water content during extrusion of 11.5 % (w/w), respectively.

The influence of water concentration during extrusion on the properties of α-lactose monohydrate tablets formulated without and with 2.5% (w/w) PVP is shown in Fig. 2 a and b, respectively. The friability varied from 0.5 to 1.0 % for tablets without PVP and from 0.6 to 0.8 % for tablets with PVP. To evaluate the influence of water concentration on tablet properties, tablets produced at a water concentration above the optimum were also included despite their suboptimal shape. There was a significant positive correlation between the water concentration during extrusion and the porosity (without PVP: r=0.792, with PVP r= 0.899) and a significant negative correlation between the water concentration during extrusion and the tensile strength (without PVP: r= -0.656, with PVP r= 0.739) and the disintegration time (without PVP: r=-0.584, with PVP r=-0.851). ANOVA analysis revealed that at the lowest water concentration tested these tablet properties were significantly different from those of tablets at the highest water concentration.

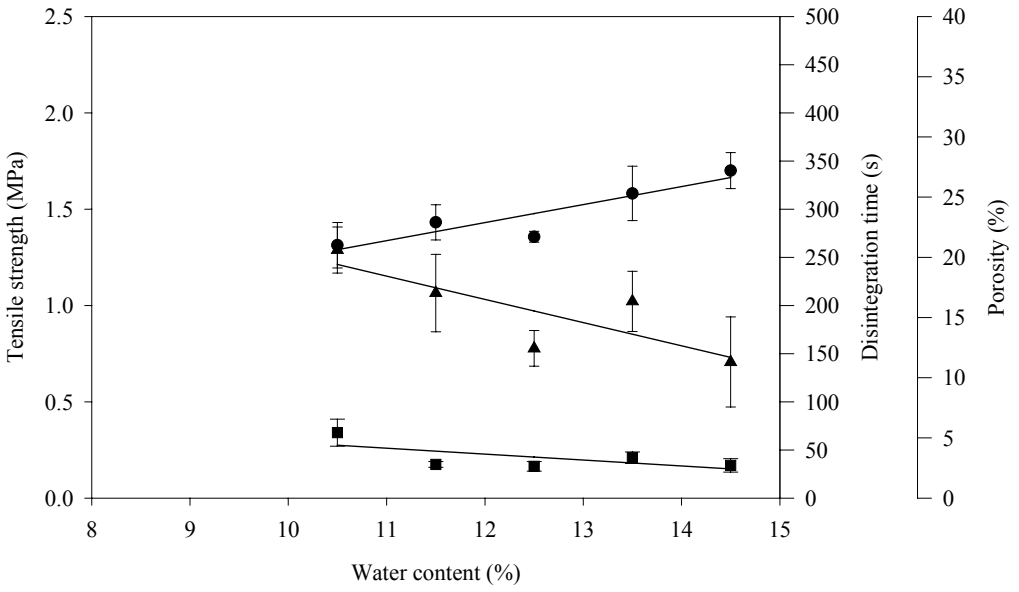


Figure 2a: Influence of the water content during extrusion on the tensile strength (▲), the porosity (●) and the disintegration time (■) of α-lactose monohydrate tablets formulated without PVP at a screw speed of 250 rpm and a total input rate of 5.6 $kg.h^{-1}$.

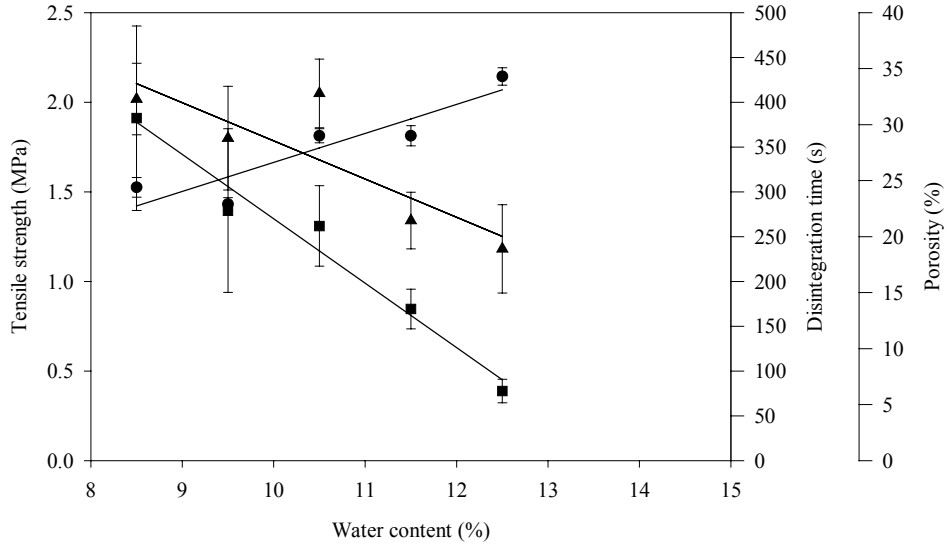


Figure 2b: Influence of the water content during extrusion on the tensile strength (▲), the porosity (●) and the disintegration time (■) of α-lactose monohydrate tablets formulated with 2.5% (w/w) PVP at a screw speed of 250 rpm and a total input rate of 5.6 $kg.h^{-1}$.

At all optimum water levels tablets with acceptable tensile strength (> 0.5 MPa), friability (< 1%) and disintegration time (< 10 min) were obtained: tablets formulated without and with PVP have a tensile strength above 0.75 and 1.85 MPa, a friability below 1.0 and 0.8 % and a disintegration time below 1 and 5 min, respectively. Comparison of the properties of tablets produced at the same water concentration but formulated without and with 2.5 % (w/w) PVP revealed that the addition of PVP significantly increased the tensile strength, the porosity and the disintegration time. It can be concluded that optimisation of the water concentration during extrusion is required for each formulation in order to allow continuous extrusion, but that within the possible working range changes in the water concentration during extrusion had only a limited influence on the tablet properties.

7.5.3 Process reproducibility

To evaluate the reproducibility of the extrusion process of α-lactose monohydrate the water concentration was maintained at 11.5 and 9.5% (w/w) for formulations without and with PVP, respectively. Table 2 shows the between-day variation (n=6) of the process evaluation parameters and of the tablet properties. All experiments were performed at a screw speed of 250 rpm and a total input rate of 5.6 $kg.h^{-1}$. Variation of the power consumption measurements was below 28%, whereas die pressure varied from 0 to 5 bar. In view of the small changes caused by varying formulation (Table 1) and process parameters (Table 3) it was clear that these parameters lack the necessary

Table 2: Between day (n=6) variation of the properties of α-lactose monohydrate tablets manufactured by cold extrusion at 250 rpm and a total input of 5.6 $kg.h^{-1}$ formulated without PVP and with 2.5% PVP (w/w) at a water content during extrusion of 11.5 and 9.5 % (w/w), respectively.

	Tablet properties			**Process evaluation parameters**	
	Tensile strength *(MPa)*	**Friability** *(%)*	**Disintegration** *(s)*	**Power consumption** *(%)*	**Die pressure** *(bar)*
a-Lactose monohydrate (water content during extrusion 11.5%[2])					
	1.02	0.87	35	23	0
	1.23	0.62	37	27	1
	0.82	0.79	32	23	2
	0.91	0.66	33	23	1
	1.01	0.74	38	23	0
	1.32	0.78	41	24	0
Avg	1.05	0.74	36	24	1
SD	0.19	0.09	3	2	1
CV%	18	12	9	7	114
a-Lactose monohydrate with 2.5%[1] PVP (water content during extrusion 9.5%[2])					
	1.68	0.5	294	25	2
	1.78	0.7	160	27	5
	2.16	0.61	423	25	5
	2.04	0.61	275	26	2
	1.85	0.55	295	20	0
	1.58	0.82	218	25	1
Avg	1.85	0.63	279	25	3
SD	0.22	0.11	91	2	2
CV%	12	18	33	10	83

[1] Based on dry weight (w/w). [2] Based on wet extruded mass (w/w).

sensitivity to be used as indicators to optimise the process and that visual evaluation is required. However, these parameters are worthwhile recording as they allow early detection of problems (die blocking, too high friction, etc.), enabling to stop the process before any damage to the extruder occurs.

For tablets, formulated without PVP, the tablet tensile strength was above 0.8 MPa, the friability below 0.9% and the disintegration time below 1 min, while tablets formulated with 2.5% (w/w) PVP had a tablet tensile strength above 1.5 MPa, a friability below 0.85% and a disintegration time below 8 min. From these results it was clear that for cold extrusion of α-lactose monohydrate formulations without as well as with PVP resulted in good quality tablets. This was in contrast to the manufacturing of α-lactose monohydrate tablets by direct compression or compression of granules, where PVP-addition or high compression forces are required to obtain acceptable tablet tensile strength and friability (Riepma et al., 1993; Bolhuis and Zuurman 1995; Juppo et al., 1995; Becker et al., 1997; Horisawa et al., 2000; Wostheinrich and Schmigt, 2000, Keleb et al., 2002). These data indicate that cold extrusion could be useful as a single step granulation and tableting technique for materials that normally require granulation.

7.5.4 Influence of process parameters

In Table 3 the process evaluation parameters obtained at different screw speeds and total input rates are presented. If for pure α-lactose monohydrate the screw speed was progressively increased above 350 rpm at a constant input rate of 5.6 $kg.h^{-1}$ blocking of the die occurred. A similar effect was observed when the total input rate was decreased to 4.5 $kg.h^{-1}$ or below at 250 rpm. In both cases the extruder load was decreased leading to an insufficient filling of the screws and a pressure too low to push the mass through the die. This induced accumulation and drying of α-lactose monohydrate at the die, leading to partial die obstruction. On the contrary, decreasing the extruder load during extrusion of α-lactose monohydrate with PVP did not result in die blockage, but a discontinuous flow of the extrudates was noticed. This indicates again the lubricating effect of PVP during cold extrusion of α-lactose monohydrate.

Table 3: Influence of the screw speed and the total input rate on the process evaluation parameters for extrusion of α-lactose monohydrate formulated without PVP and with 2.5% (w/w) PVP at a water content during extrusion of 11.5 and 9.5 % (w/w), respectively.

Formulation		Process parameters		Process evaluation parameters		
PVP *(%)*	**Water** *(%)*	**Total feed rate** *(kg./h)*	**Screw speed** *(rpm)*	**Power consumption** *(%)*	**Die pressure** *(bar)*	**Remarks**
0	11.5	5.6	200	27	0	
			250	24*	1*	
			300	24	0	
			350	16	0	
			400	>90	>15	Die blocking
			450	>90	>15	Die blocking
2.5	9.5	5.6	200	28	3	
			250	25*	3*	
			300	24	1	
			350	25-27	1	Discontinuous extrudate flow
			400	23-31	1	Discontinuous extrudate flow
			450	22-30	1	Discontinuous extrudate flow
0	11.5	3.5		>90	>15	Die blocking
		4.5		>90	>15	Die blocking
		5.6		24*	1*	
		6.5		26	3	
		7.5				Powder accumulation at inlet
2.5	9.5	3.5		21-25	0-5	Discontinuous extrudate flow
		4.5		22-25	0-7	Discontinuous extrudate flow
		5.6		25*	3*	
		6.5		26	2	
		7.5				Powder accumulation at inlet

*Average of 6

This was also reflected in the large within-run variation of the power consumption and die pressure. Increasing the total input rate to 7.5 $kg.h^{-1}$ at a constant screw speed of 250 rpm, resulted in screw overloading. In order to obtain a higher throughput the total input rate as well as the screw speed have to be increased. These findings indicated that in this extrusion process the full screw transport capacity must be used and that the feed rate should be optimised in order to prevent die blocking and to guarantee a continuous discharge of the extrudate.

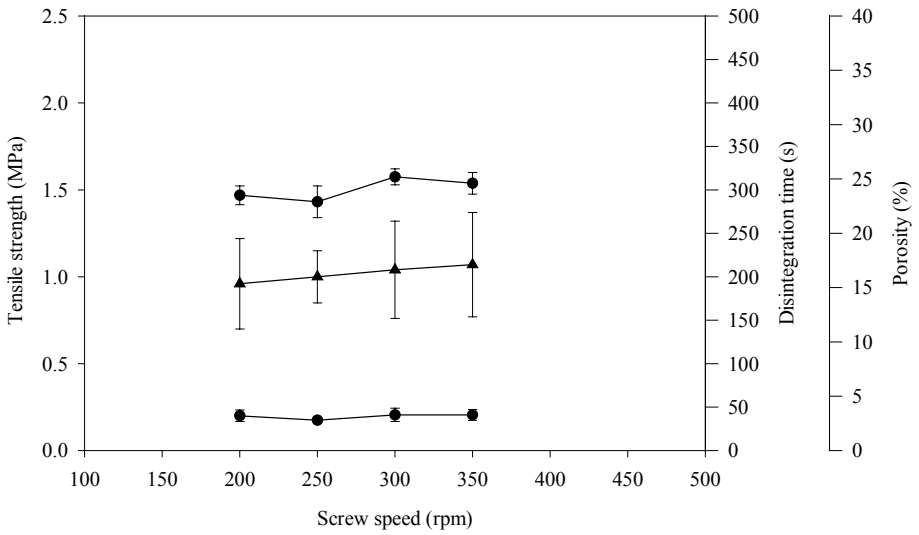


Figure 3a: Influence of the screw speed on the tensile strength (▲), the porosity (●) and the disintegration time (■) of α-lactose monohydrate tablets formulated without PVP at a water concentration during extrusion of 11.5 % (w/w) and a total input rate of 5.6 $kg.h^{-1}$.

The total input rate did not affect tablet properties, even if it was decreased from 6.5 to 3.5 $kg.h^{-1}$ at a constant screw speed of 250 rpm. It is also important to notice that tablet properties remained the same even if the extrudate output was discontinuous. Fig. 3 shows the influence of the screw speed on the properties of α-lactose monohydrate tablets formulated without (a) and with PVP (b). The friability varied from 0.65 to 0.99% for tablets without PVP and from 0.5 to 1.07% with PVP, but was always below 1% at conditions that allowed continuous tablet production. The screw speed also had no effect on the properties of tablets formulated without PVP, while there was a significant positive correlation between screw speed and porosity (r=0.843) and a significant negative correlation between screw speed and tensile strength (r=-0.632) and disintegration time (r=-0.844) for tablets formulated with PVP. ANOVA analysis revealed that varying the screw speed only resulted in significant differences for disintegration time and porosity. This difference between the effect of screw speed on the disintegration time of tablets formulated without and with 2.5% (w/w) PVP could be due

to the higher viscosity of the liquid phase penetrated into the pores in the presence of PVP. This increase in viscosity will dramatically affect the penetration rate of the liquid into the tablet. In this case disintegration is probably mainly determined by the amount of liquid that can penetrate into the tablet and is thereby strongly affected by changes in porosity. For tablets without PVP the disintegration is probably mainly determined by the dissolution rate of α-lactose monohydrate. As α-lactose monohydrate is soluble in water, the disintegration is not affected by the changes in porosity.

From these experiments it can be concluded that the screw speed as well as the total input rate should be optimised to allow continuous processing. Varying of these parameters within the optimum working range did not affect the tablet quality, except for the screw speed which influenced the disintegration time of tablets formulated with 2.5% (w/w) PVP.

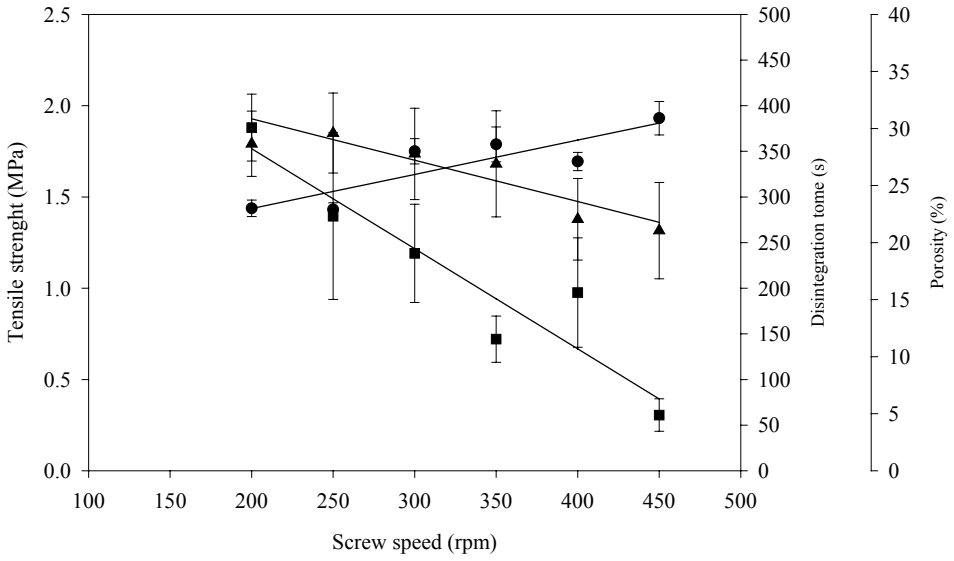


Figure 3b: Influence of the screw speed on the tensile strength (▲), the porosity (●) and the disintegration time (■) of α-lactose monohydrate tablets formulated with PVP at a water concentration during extrusion of 9.5 (w/w) and a total input rate of 5.6 $kg.h^{-1}$.

7.5.5 Cold extrusion and the incorporation of drugs

Incorporation of 10% hydrochlorothiazide in α-lactose monohydrate tablets formulated without and with 2.5% (w/w) PVP had no effect, neither on the process feasibility nor on the tablet properties. All tablets containing hydrochlorothiazide formulated without and with 2.5% (w/w) PVP had a tablet tensile strength above 1.1 and 1.7 MPa, a friability below 0.85 and 0.8% and a disintegration time below 1 and 5 min, respectively. Content uniformity measurements revealed that each tablet contained between 95 and 105% of the theoretical concentration. All tablets containing hydrochlorothiazide complied with the USP XXIII dissolution specifications (60% dissolved within 30 min): 73 and 71% hydrochlorothiazide being released after 10 min from tablets without and with PVP, respectively.

7.5.6 Comparison of α-lactose monohydrate tablets prepared by direct compression and by cold extrusion

The properties of α-lactose monohydrate tablets prepared by direct compression and by cold extrusion are shown in Fig 4a. Tablets prepared by extrusion have a significantly higher porosity and have larger pores than those prepared by compression.
This difference could explain the significantly faster disintegration of tablets prepared by extrusion. However, the tensile strength of tablets prepared by extrusion is not significantly different to that of tablets prepared by direct compression. These differences in tablet properties could be explained by a different bonding mechanism involved in the different tablet manufacturing techniques used. During cold extrusion only limited compression of the material occurs, while the dissolved α-lactose monohydrate fraction will crystallise on drying forming solid bridges. During mechanical compression of α-lactose monohydrate the applied forces are much higher and will cause α-lactose monohydrate to fragment and to bind mainly through intermolecular bonds (hydrogen bonds and Van der Waals interactions).

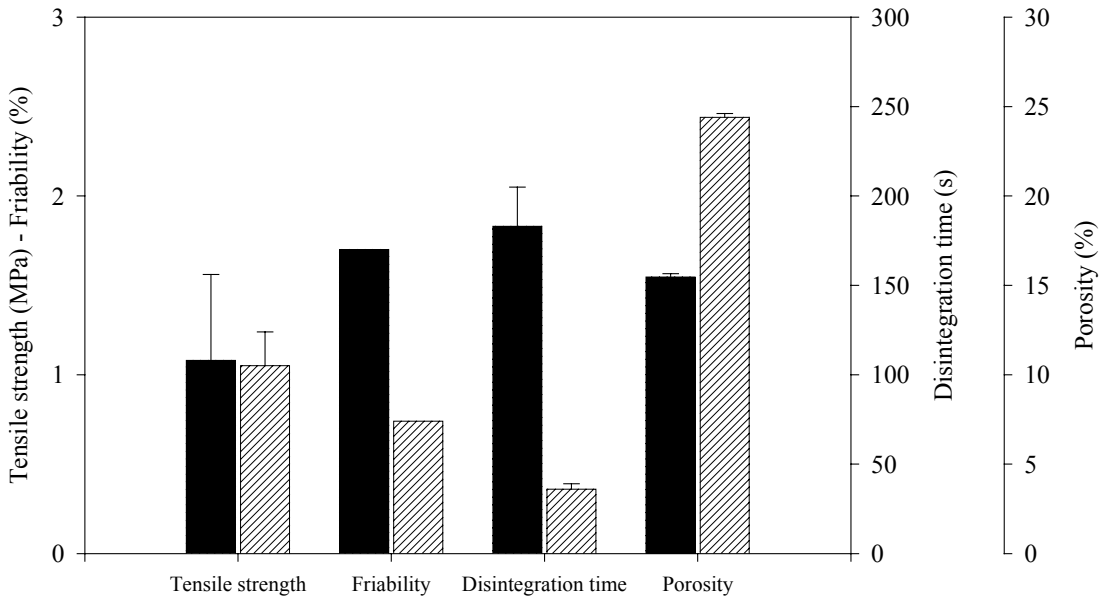


Figure 4a: Tensile strength, porosity, friability and disintegration time of α-lactose monohydrate tablets prepared by direct compression (■) (9 mm diameter, 250 mg, 10 kN) and cold extrusion (▨) (water concentration during extrusion 11.5 % (w/w), screw speed 250 rpm and total input rate 5.6 $kg.h^{-1}$).

However, these intermolecular bonds are much weaker (1-10 kcal/mol) than solid bridges (50-200 kcal/mol) (Nystrom et al., 1993). The similar tensile strength of tablets prepared by cold extrusion and by direct compression indicated that the intermolecular bonds formed during compression are more numerous compared to the solid bridges formed during cold extrusion. This is confirmed by the porosity data (Fig. 4b) and by SEM pictures (Fig. 5) which clearly show that tablets prepared by extrusion have much larger pores than conventional tablets prepared by compression. The strength of solid bridges is mainly determined by the amount of solids deposited in the solid bridges and by the rate of crystallisation (Khankari and Hontz, 1997). Both factors are more likely to be affected by formulation variables such as water content during extrusion and PVP addition than by process parameters. This could explain the fact that tensile strength is only affected by changes in water concentration during extrusion and PVP addition, but not by varying the

process parameters. These data clearly show that cold extrusion results in tablets with similar tensile strength, with a higher porosity and a lower disintegration time compared to conventional tablets prepared by direct compression. Similar phenomena i.e. a higher porosity and faster disintegration time for the same tensile strength as tablets prepared by compression were seen by Bi et al. (1999) after wet compression of α-lactose monohydrate granules. However, to obtain tablets with acceptable tensile strength a compression force above 500 kN, which is much higher than the compression force routinely used in tablet production, was required.

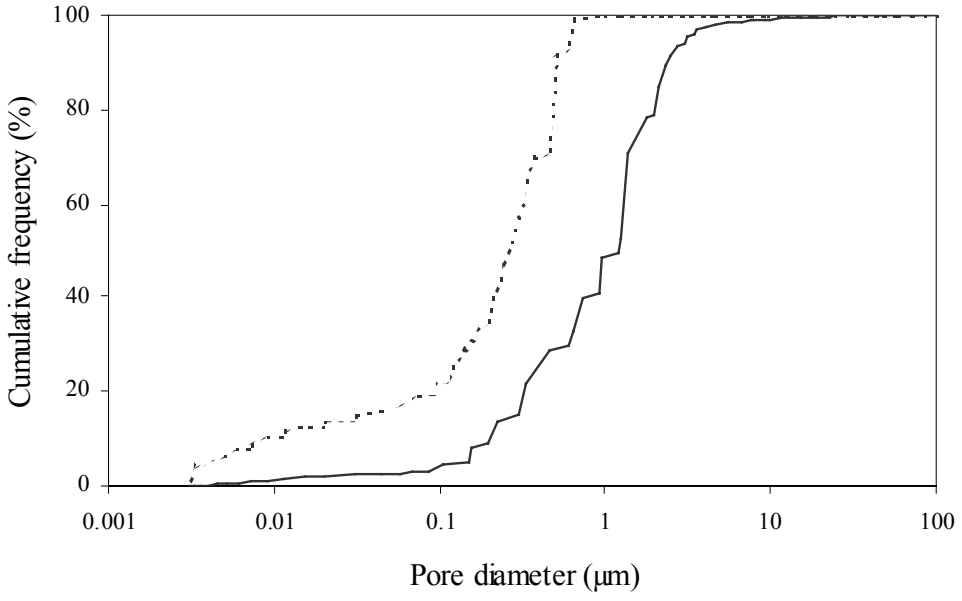
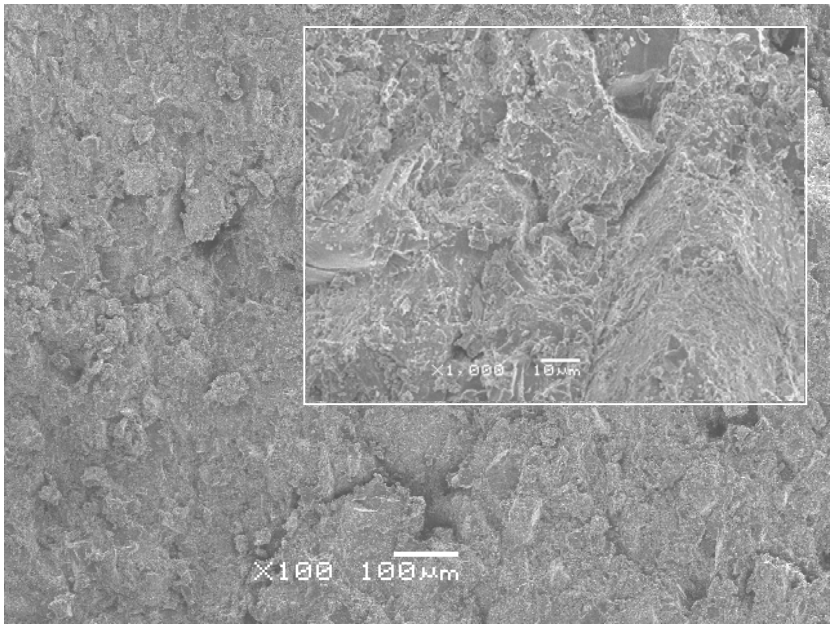


Figure 4b: Pore size distribution of α-lactose monohydrate tablets prepared by direct compression (----) (9 mm diameter, 250 mg, 10 kN) and cold extrusion (—) (water concentration during extrusion 11.5 % (w/w), screw speed 250 rpm and total input rate 5.6 $kg.h^{-1}$).

a



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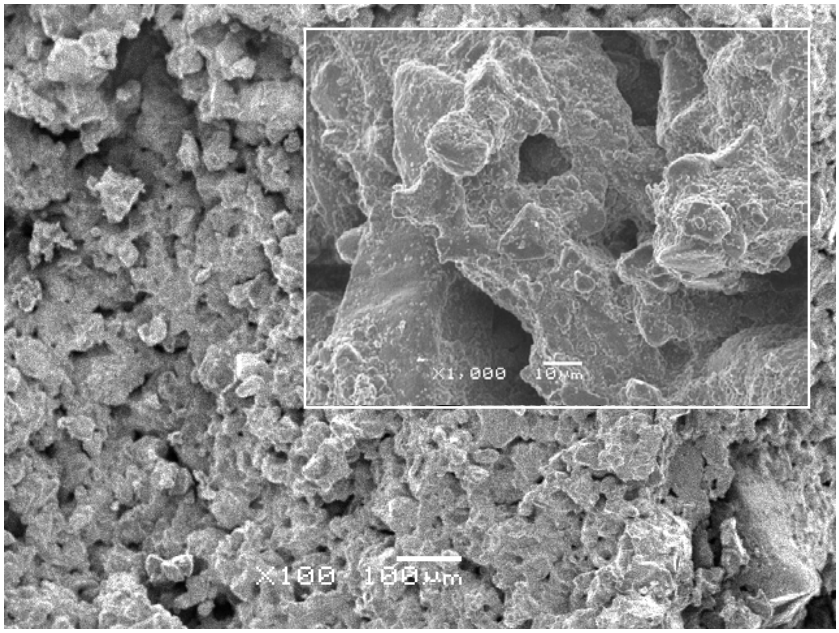

Figure 5: SEM pictures of α-lactose monohydrate tablets prepared (a) by direct compression (9 mm diameter, 250 mg, 10 kN) and (b) by cold extrusion (water concentration during extrusion 11.5 % (w/w), screw speed 250 rpm and total input rate 5.6 $kg.h^{-1}$).

7.6 Conclusion

From this study it is clear that cold extrusion allows single step continuous tableting of pure α-lactose monohydrate, in contrast to conventional tableting which requires high compression force or PVP addition. Optimisation of the formulation and the process parameters is a prerequisite for the feasibility of the process, but these parameters had only a minor influence on the tablet properties under conditions which allow continuous tablet production. The high porosity of tablets prepared by cold extrusion indicates that this technique might also be suited for the tablet production of formulations with poor disintegration properties.

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8 Single-step granulation/tabletting results in strong and fast-disintegrating tablets: mechanism

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8.1 Introduction

Recently, single-step granulation/tabletting was reported as an interesting alternative for conventional granulation followed by compression (Keleb et al. 2001). This technique resulted in strong and fast disintegrating tablets with a higher porosity and larger pores than obtained by compression and allowed to avoid problems associated with compression and scaling-up. For different types of lactose single-step granulation/tabletting resulted in tablets with a higher tensile strength and faster disintegration than obtained by compression of granules prepared by high-shear granulation (Keleb et al. 2004). Single-step granulation/tabletting also resulted in strong and fast disintegrating tablets for highly dosed drugs with inherent difficulties in tablet manufacturing such as poor compressibility (e.g. paracetamol) and poor flow and disintegration properties (e.g. cimetidine) (Chapter 10). Similar tablet properties, namely a high tensile strength and fast disintegration, were reported after wet compression of α-lactose monohydrate (Bi et al. 1999). The fast disintegration was attributed to the more porous structure. The higher tensile strength, despite the relatively high porosity, was suggested to be due to a different mechanism of tablet formation i.e. by solid bridges rather than by intermolecular distance forces, such as Van der Waals attraction forces and hydrogen bonding the main forces involved in α-lactose monohydrate tablets made by compression. It was therefore thought reasonable to assume that solid bridges are the dominating bonding mechanism involved in tablets prepared by single-step granulation/tabletting. Several methods have been described to calculate the dominating interparticulate bonding mechanism in a compact (Adolfsson et al., 1999; Nystrom and Karehill, 2001). Recently, Olsson and Nyström (2001) proposed an interaction factor to provide qualitative information on the dominating bond types in tablets. The interaction factor is expected to be higher for tablets in which bonding occurs mainly through strong bonds (i.e. solid bridges) than for tablets in which bonding occurs solely by weaker forces (i.e. distance forces). Although the interaction factor could indicate the involvement of

strong bond types, its value to identify these strong bond types as solid bridges is limited. The mechanism of bonding or bond type has been assessed in several ways. Compacting tablets or evaluating the strength of tablets in media with differing dielectric constants were used to investigate the contribution of intermolecular attraction forces (Olsson et al. 1996; Luangtana-Anan and Newton 1990), while electrical conductivity measurements showed to be a valuable tool to prove the presence of solid bridges in tablets (Bhatia and Lordi, 1979).

The purpose of this study was to explain the high tensile strength and fast disintegration of tablets prepared by single-step granulation/tabletting by analysing the internal tablet structure and determination of the bonding mechanism. To evaluate whether the internal tablet structure and the bonding mechanism are affected by the formulation, formulations with different physical properties were analysed.

8.2 Materials

α-Lactose monohydrate 200M (aqueous solubility: 1 in 4.6, particle size: 98% < 150μm) (DMV, Veghel, The Netherlands) was used as an excipient. Paracetamol (aqueous solubility: 1 in 70, particle size: 98% < 600 μm) (Mallinckrodt Inc., Capitol Boulevard, NC, USA) and cimetidine (aqueous solubility: 1 in 88, particle size: 100% < 250μm) (Roig Farma S.A., Barcelona, Spain) were used as drugs with poor compactibility and poor flow and disintegration properties, respectively. Polyvinylpyrrolidone (PVP, Kollidon® K30, BASF, Ludwigshafen, Germany) was used as a binder.

8.3 Methods

8.3.1 Single-step granulation/tabletting

Single-step granulation/tabletting was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1 and equipped with a standard screw profile having two mixing sections and a circular 9 mm die attached to the extruder outlet (Keleb et al., 2001). Processing parameters were set at 25°C barrel temperature, 250 rpm screw speed and 5.6 kg/h total input rate (powder feed rate + liquid feed rate). The powder

(α-lactose monohydrate, paracetamol and cimetidine or a mixture of one of these drugs with α-lactose monohydrate) was fed on top of the screws using a twin screw feeding system. Drug/excipient mixtures were previously blended for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the extruder barrel by means of a peristaltic pump (Watson Marlow Type 505L, Cornwall, UK). The water concentration during extrusion was optimized for each formulation and was 9.5 and 11.5% (w/w) for α-lactose monohydrate with and without PVP, respectively; 10.5 and 9.5% (w/w) for the formulations containing 97.5 and 80% (w/w) paracetamol, respectively and 14.5% (w/w) for all formulations containing cimetidine. All water concentrations were calculated based on the wet extruded mass, whereas all PVP and drug concentrations were calculated based on dry tablet weight. In order to ensure equilibration of the extruder at the test conditions, samples were only taken 10 min after the process was started. Immediately after extrusion tablets (thickness: 4 mm) were manually cut using surgical blades. The tablets were oven-dried at 25°C for 20 h.

8.3.2 Granulation

The extrusion/granulation was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1 and equipped with two standard screws and die block (Keleb et al., 2002). The extruder was set at a constant temperature of 25°C. Processing conditions during extrusion were: a screw speed of 250 rpm and a total input rate of 5.6 kg/h. The water concentration during extrusion was 7.5% (w/w). The powder (α-lactose monohydrate, paracetamol and cimetidine or a mixture of one of these drugs with α-lactose monohydrate) was fed on top of the screws using a twin screw feeding system. Drug/excipient mixtures were previously blended for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). The granulation liquid (pure water or an aqueous PVP solution) was pumped into the first zone of the extruder barrel by means of a peristaltic pump (Watson Marlow type 505L, Cornwall, UK). At the end of the extruder barrel large extrudates were obtained. Those extrudates (400 g) were immediately wet sized using a 1 mm oscillating sieve (Frewitt, Fribourg, Switzerland), operated at a minimal distance between rotor and

sieve. In order to ensure equilibration of the extruder at the test conditions, samples were collected only 10 min after the process was started.

High shear granulation was performed in a Gral 10 (Machines Collette, Wommelgem, Belgium). The granulation process was performed at 500 rpm impeller speed, 3000 rpm chopper speed, a total load of 0.16 kg/l and 10% (w/w) water concentration. After mixing the powder for 2 min, the required amount of granulating liquid was continuously added over a period of 10 min using a peristaltic pump (Watson Marlow, Cornwall, UK). Wet massing was continued for 2 min following complete liquid addition. The granules were oven dried at 25°C for 20 h.

8.3.3 Compression

Granules ($F_{250\text{-}710\ \mu m}$) were blended with 0.5% (w/w) magnesium stearate (<90 μm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland) for 1 min. Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN. Similarly, the powder mixtures were compressed into tablets after mixing with 0.5% (w/w) magnesium stearate (<90 μm). Tablets intended for electrical conductivity measurements were prepared without magnesium stearate as this compound dramatically decreased the conductivity. For the preparation of these tablets die lubrification with a magnesium stearate solution (1%, w/v) in ethanol was performed.

8.3.4 Tablet characterisation

The same methods as described in Chapter 3 were used to determine the tensile strength and disintegration time of the tablets. The same method as used in Chapter 4 was used to determine the porosity of the tablets and the internal structure of the tablets was evaluated by scanning electron microscopy (SEM) (JSM 5600 LV scanning electron microscope, JEOL Europe, Zaventem, Belgium).

8.3.4.1 Measurement of total pore surface area (BET)

Specific surface area of the granules was measured in triplicate using nitrogen adsorption (Gemini, Micromeretics). The samples were vacuum dried for 60 min

before analysis. The specific surface area was calculated according to the BET equation.

8.3.4.2 Electrical conductivity measurements

A schematic diagram of the system used to measure the electrical resistivity of the tablets is shown in figure 1. A Cu-plate of 8 cm diameter and 0.8 cm thickness was attached to a teflon block. On top of the Cu-plate and on both sides of the tablets, Ag-paste (Acheson Electrodag 1415M, Rotterdam, The Netherlands) was applied to obtain good electrical contact between the sample and the electrometer. Two contact needle electrodes were used to measure conductance through the tablets. One electrode made contact with the Cu-plate, the second one was contacted to the tablet. The height of the needle could be varied to obtain good contact with the tablets. In parallel, a 10 V battery was connected. A shielded cable connected the needle electrodes to the electrometer (Keithly 610B, Cleveland, Ohio, USA). Stable values were obtained within 1 min. of recording. The accuracy of the measurements was checked by connecting standard resistors (1 MOhm-10 GOhm) between the electrodes and the plate. For each tablet type, a minimum of five tablets was measured to obtain statistical significance. The reported values are averages of replicated runs. Sample dimensions were recorded with a micrometer.

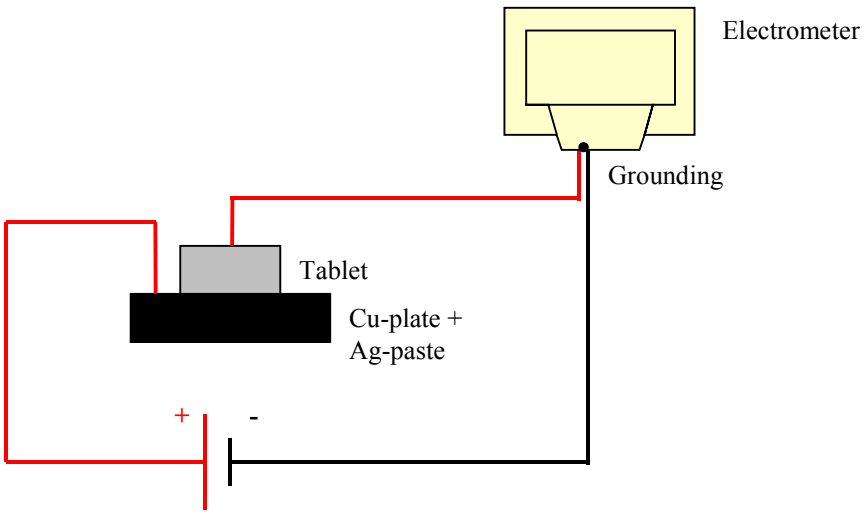


Figure 1: Schematic diagram of the system used to measure the electrical resistivity of the tablets.

The specific resistance was calculated from the measured currents and the dimensions of the tablets according to:

$$\text{Specific resistance} = \frac{V.\ \text{Tablet thickness}}{I.\ \text{Punch area}} \qquad (\Omega.\text{cm}) \qquad (3)$$

Where I is the measured current (A) and V is the voltage of the battery (10V).

8.3.4.3 Determination of dominating bonding mechanism

The dominating bonding mechanism was determined by calculating the interaction factor (σ_b*) as follows:

$$\sigma_t / (1-\varepsilon) * S \qquad (4)$$

in which σ_t is the tablet tensile strength, ε is the tablet porosity and S is the specific surface area. The thus obtained value (σ_b*) should be regarded as a qualitative description of the bond types in the tablet, and not a quantitative value of average bond strength. The interaction factor (σ_b*) is expected to be higher for tablets in which bonding occurs mainly by strong bonds (i.e. solid bridges) than for tablets in which bonding occurs solely by weaker forces (i.e. distance forces).

8.4 Statistical analysis

Before any analysis was performed, the data were tested for normal distribution with the Kolmogorov-Smirnov test and the homogeneity of variances was tested with the Levene's test. The influence of the production process on the tablet characteristics was determined using one-way ANOVA ($P < 0.05$). To further compare the effects of different production processes, a multiple comparison among pairs of means was performed using the Scheffé test with $P < 0.05$ as a significance level. For all statistical analyses, the computer program SPSS version 11.0 was used.

8.5 Results and discussion

Table 1 presents the tensile strength, the disintegration time, the porosity and the specific surface area obtained for tablets manufactured using the different processes. As tablets containing 97.5% (w/w) paracetamol could only be manufactured by single-step granulation/tabletting, tablets containing 80% (w/w) paracetamol were prepared to compare the different techniques. Single-step granulation/tabletting resulted in a higher tensile strength than obtained with the other manufacturing techniques, except in the case of cimetidine tablets. In all cases tablets manufactured by single-step granulation/tabletting had a similar or lower disintegration time. The faster disintegration could be explained by differences in internal tablet structure. Porosity and BET measurements revealed that tablets made by single-step granulation/tabletting had a similar or higher porosity and a similar or lower surface area. These data indicated that larger pores were present in tablets manufactured by single-step granulation/tabletting than in compressed tablets. This was in agreement with a previous study showing that the pore size of α-lactose monohydrate tablets prepared by single-step granulation/tabletting was 10-fold larger than in tablets manufactured by direct compression (Keleb e al., 2001). The differences in pore structure were also obvious from the SEM pictures of the tablet fracture planes (Fig. 2). Tablets manufactured by single-step granulation/tabletting showed a more porous, sponge-like structure, while compressed tablets showed a more dense structure. In all cases differences in internal tablet structure could explain the superior disintegration properties.

As tablets produced by single-step granulation/tabletting had larger pores, their higher tensile strength could not be attributed to a larger number of bonds. Therefore, it was assumed that a stronger bond type was involved. Determination of the interaction factor confirmed this hypothesis. For each formulation studied a higher interaction factor was obtained for tablets manufactured by single-step granulation/tabletting than for compressed tablets, except for tablets containing cimetidine (Fig. 3).

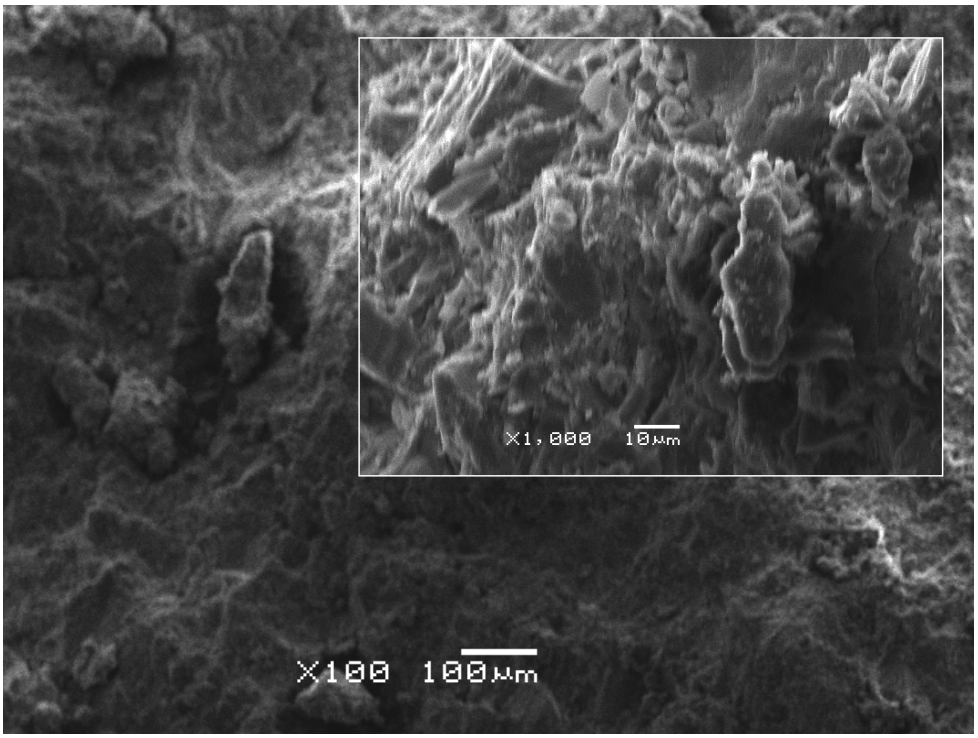
Electrical conductance measurements revealed for all tablets manufactured by single-step granulation/tabletting a significantly lower specific resistivity than for compressed tablets (Fig. 4), indicating that solid bridges were involved. This was confirmed by SEM pictures (Fig. 2), showing that in tablets prepared by single-step

Table 1: Properties of tablets prepared by different manufacturing techniques.

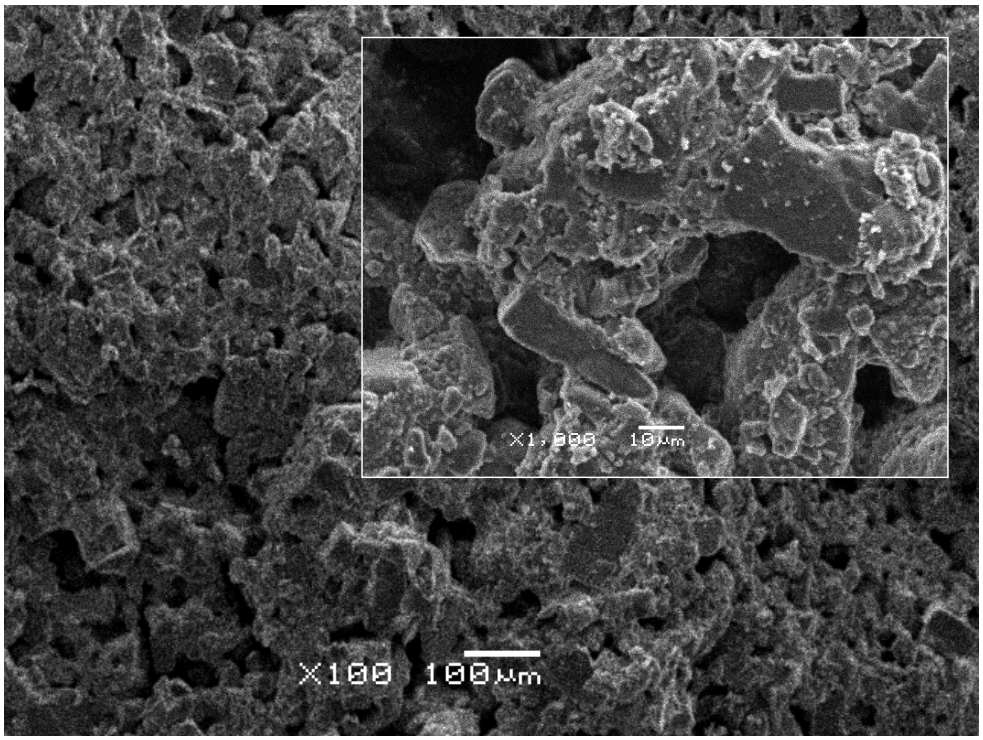
Formulation	Tablet production process	Tensile strength (MPa)	Disintegration time (s)	Porosity (%)	Specific surface area (m^2/g)
α-Lactose monohydrate	Single-step granulation/tabletting	1.00 ± 0.15^{a}	35 ± 3^{a}	22.9 ± 1.46^{a}	0.98 ± 0.01^{a}
	High shear granulation + compression	0.67 ± 0.05^{b}	83 ± 16^{b}	14.5 ± 1.08^{b}	1.73 ± 0.00^{b}
	Extrusion granulation + compression	0.50 ± 0.04^{b}	12 ± 24^{c}	13.5 ± 0.61^{b}	1.74 ± 0.01^{b}
	Direct compression	0.89 ± 0.17^{a}	161 ± 9^{d}	14.2 ± 1.70^{b}	1.84 ± 0.01^{c}
α-Lactose monohydrate (97.5%), PVP (2.5%)	Single-step granulation/tabletting	1.85 ± 0.22^{a}	279 ± 91^{a}	22.9 ± 0.58^{a}	1.00 ± 0.06^{a}
	High shear granulation + compression	0.91 ± 0.07^{b}	266 ± 32^{a}	20.2 ± 0.83^{a}	0.97 ± 0.00^{b}
	Extrusion granulation + compression	0.79 ± 0.05^{b}	615 ± 50^{b}	21.3 ± 0.95^{a}	1.78 ± 0.00^{c}
	Direct compression	0.70 ± 0.08^{b}	311 ? 39^{a}	18.3 ± 0.60^{a}	1.80 ± 0.01^{c}
Paracetamol (97.5%), PVP (2.5%)	Single-step granulation/tabletting	0.92 ± 0.09^{a}	593 ± 107^{da}	22.1 ± 2.04^{a}	1.37 ± 0.01^{a}
Paracetamol (80%), α-lactose monohydrate (17.5%),	Single-step granulation/tabletting	1.39 ± 0.22^{b}	184 ± 50^{b}	22.0 ± 0.40^{a}	1.35 ± 0.03^{a}
PVP (2.5%	High shear granulation + compression	0.75 ± 0.13^{a}	2799 ± 145^{c}	14.7 ± 0.86^{b}	0.98 ± 0.00^{b}
	Extrusion granulation + compression	0.95 ± 0.14^{a}	1712 ± 250^{d}	19.5 ± 0.32^{c}	1.44 ± 0.01^{c}
	Direct compression	-	-	-	-
Cimetidine (97.5%), PVP (2.5%)	Single-step granulation/tabletting	0.85 ± 0.17^{a}	638 ± 267^{a}	30.7 ± 1.40^{a}	2.27 ± 0.01^{a}
	High shear granulation + compression	1.83 ± 0.19^{b}	$> 3600^{b}$	8.9 ± 2.30^{b}	1.85 ± 0.01^{b}
	Extrusion granulation + compression	1.86 ± 0.21^{b}	$> 3600^{b}$	15.1 ± 0.09^{c}	2.55 ± 0.01^{c}
	Direct compression	0.89 ± 0.14^{a}	$> 3600^{b}$	7.9 ± 2.10^{b}	2.08 ± 0.01^{d}
Cimetidine (80%), α-lactose monohydrate (17.5%), PVP (2.5%)	Single-step granulation/tabletting	1.30 ± 0.16^{c}	198 ± 25^{c}	25.5 ± 1.08^{d}	2.28 ± 0.03^{a}

^{a,b,c,d} values within the same group having the same subscript were not significantly different (Scheffé test, $p < 0.05$).

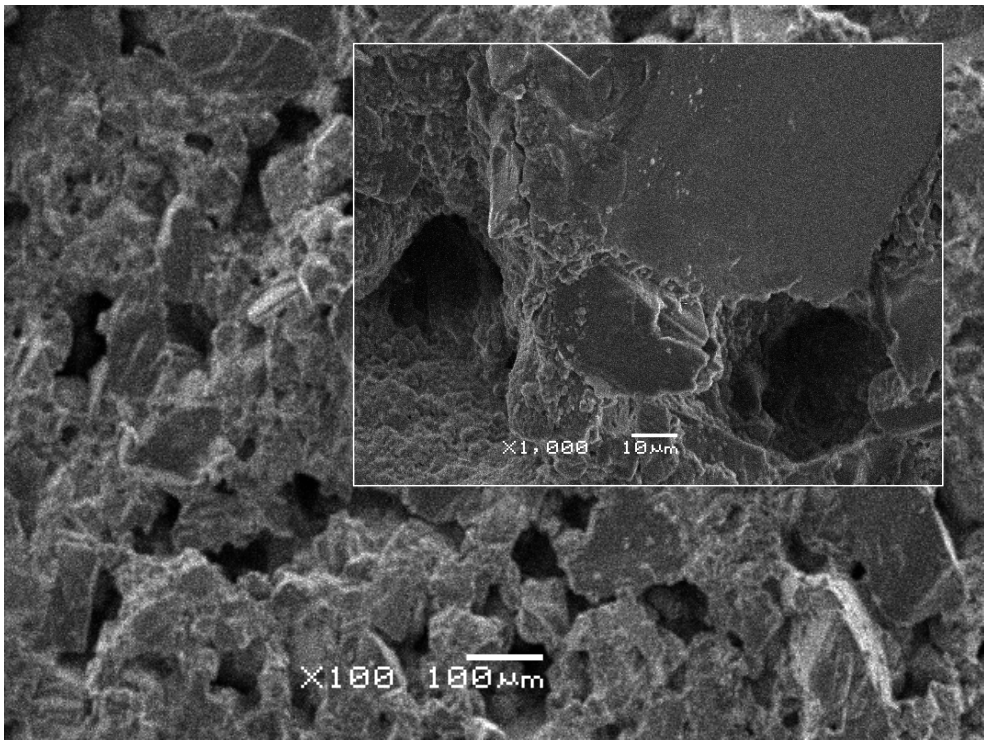
a: α-lactose monohydrate (97.5%, w/w) and PVP (2.5%, w/w) prepared by high shear granulation followed by compression



b: α-lactose monohydrate (97.5%, w/w) and PVP (2.5%, w/w) prepared by single-step granulation/tabletting



c: tablets containing paracetamol (80%, w/w), α-lactose monohydrate (17.5%, w/w) and PVP (2.5%, w/w) prepared by single-step granulation/tabletting



d: cimetidine (97.5%, w/w) and PVP (2.5%, w/w) prepared by single-step granulation/tabletting

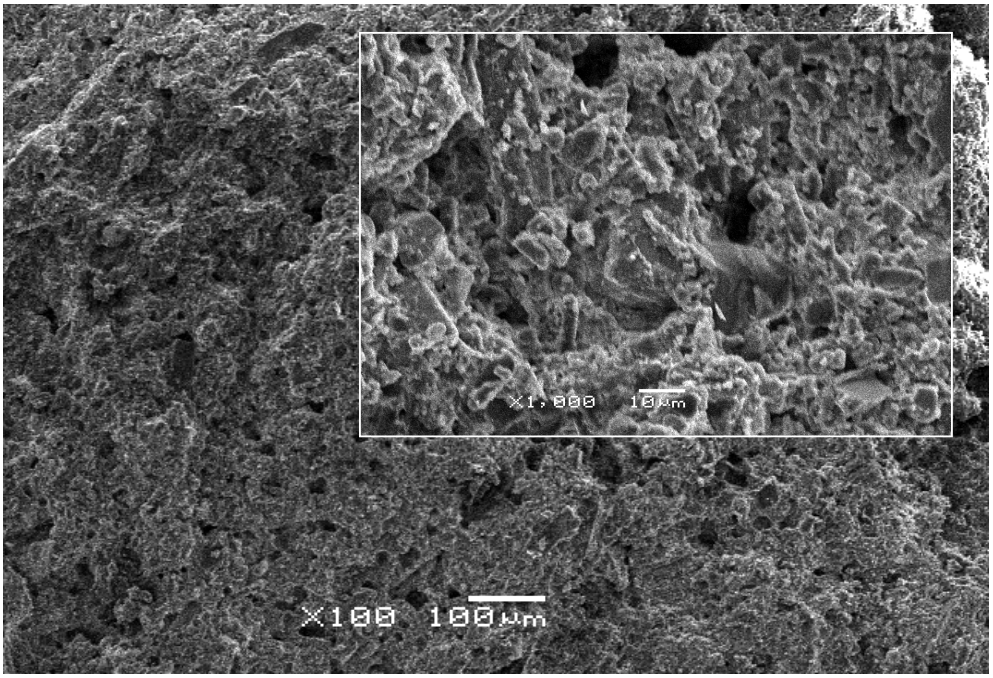


Figure 2: SEM pictures of tablets.

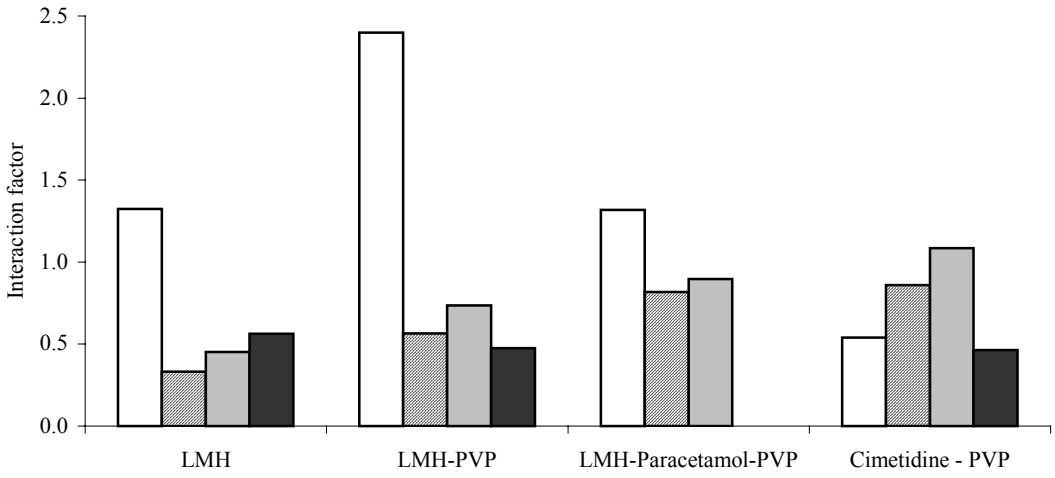


Figure 3: Interaction factor for tablets consisting of pure α-lactose monohydrate, α-lactose monohydrate and PVP (2.5%, w/w), α-lactose monohydrate, paracetamol (80%, w/w) and PVP (2.5%, w/w), and cimetidine and PVP (2.5%, w/w) prepared by single-step granulation/tabletting (□), extrusion granulation + compression (▨), high shear granulation + compression (▩) and direct compression (■).

granulation/tabletting the particles were glued together by solid bridges formed by solidification of dissolved excipient and/or drug particles.

Comparison of the characteristics of tablets of different formulations manufactured by single-step granulation/tabletting revealed differences in tablet strength, porosity, disintegration time, total pore surface area as well as differences in interaction factor. SEM pictures also showed different internal structure of these tablets (Fig. 2). In an attempt to explain these differences, the characteristics of paracetamol and cimetidine tablets with the same drug concentration (both drugs have a similar solubility, but a different particle size) and those of pure cimetidine and lactose tablets with PVP (cimetidine and α-lactose monohydrate have a similar particle size, but a different solubility) were compared. Comparison of formulations with a different solubility revealed that a lower solubility resulted in a lower tensile strength, a higher disintegration time, a higher specific surface area and a lower interaction factor (i.e. an interaction factor of 0.54 and 1.24 for tablets containing 97.5% (w/w) cimetidine and paracetamol, respectively, and 2.40 for tablets containing 97.5% (w/w) α-lactose monohydrate). These differences are due to the tablet binding mechanism during

single-step granulation/tabletting as a soluble (lactose) dissolves to a larger extent during processing and on subsequent drying more solid bridges are formed. These results were in agreement with Khankari and Hontz (1997) who reported that the strength of solid bridges is mainly determined by the amount of solids deposited in the solid bridges. However, it should be emphasized that even for these formulations with less solid bridge formation during single-step granulation/tabletting (due to the poor solubility of the component), tablets with acceptable strength were obtained. Comparison of the cimetidine and paracetamol formulations revealed that particle size had an important effect on the interaction factor. This is also due to the tablet formation mechanism during single-step granulation/tabletting as the particles of these poorly soluble formulations will only dissolve partially and the original particle size will determine the pore structure of the tablet (larger pores being obtained for formulations having a larger particle size).

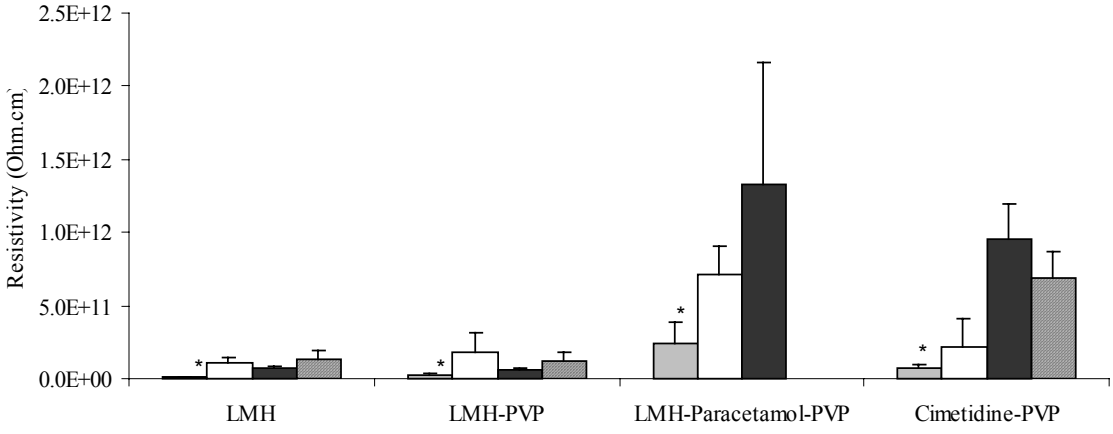


Figure 4: Resistivity (mean ± s.d., n= 5- 7) of tablets consisting of pure α-lactose monohydrate, α-lactose monohydrate and PVP (2.5%, w/w), α-lactose monohydrate, paracetamol (80%, w/w) and PVP (2.5%, w/w), and cimetidine and PVP (2.5%, w/w) prepared by single-step granulation/tabletting (▒), extrusion granulation + compression (□) , high shear granulation + compression (■) and direct compression (▨). (*) Significantly different from other values in the same group (Scheffé test, $P<0.05$)

Hence fewer but larger solid bridges will be formed, explaining the larger interaction factor for paracetamol. The similar tensile strength of 97.5% (w/w) paracetamol and cimetidine tablets, despite their different interaction factor, could be explained by a higher number of solid bridges formed in the cimetidine tablets. This again confirmed the proposed mechanism of tablet formation.

8.6 Conclusion

During single-step granulation/tabletting solid bridges are the predominant bonding mechanism involved in tablet formation. The physical properties of the formulation clearly affected the tensile strength and the internal structure, but this never resulted in an unacceptable tablet quality. This is in contrast to tabletting techniques involving compression, whereby the material properties determine the dominating bond type and can have a detrimental effect on the tablet properties.

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9 Single step granulation/tabletting of different grades of lactose: a comparison with high shear granulation

Accepted for publication in Eur. J. Pharm. Biopharm.

9.1 Introduction

Recently a novel tabletting method, called single-step granulation/tabletting, was developed and described by Keleb et al.(2001*)*. This technique not only allowed continuous production, but also yielded stronger and faster disintegrating tablets than conventional granulation/tabletting. Further investigation of α-lactose monohydrate tablets produced by this technique revealed that tablet formation by single-step granulation/tabletting is mainly due to formation of solid bridges between particles without major particle deformation or fracture (Keleb et al., 2001; Vermiere et al., 2004). Therefore, the particle properties may have an influence on the tablet formation and tablet properties.

Lactose is the most widely used excipient in tablet formulation and available in different grades. Lactose exists in two isomeric forms and can be either crystalline or amorphous. These two polymorphic types of lactose possess different properties such as solubility, density, melting point and hardness. In addition the different types of lactose are available in different particle size. It is well-known that the different lactose grades have different granulation and compression properties (Lerk, 1993). The first aim of this study was to investigate the influence of the physical properties of lactose on the single-step-granulation/tabletting process and on the properties of tablets obtained using this process and to compare the quality of those tablets with tablets produced by compression after high shear granulation. In addition the stability of α-lactose monohydrate 200M tablets prepared by single-step granulation/tabletting was evaluated.

9.2 Materials

The different grades of lactose used were: crystalline α-lactose monohydrate (Pharmatose® 450M, Pharmatose® 200M, Pharmatose® 100M, Pharmatose® 90M), anhydrous β-lactose (Pharmatose® DCL 21) and spray dried lactose (Pharmatose®

DCL 11), all obtained from DMV (Veghel, The Netherlands). The physical properties of the different grades of lactose used are listed in Table 1. Polyvinylpyrrolidone (PVP, Kollidon® K30) was received from BASF (Ludwigshafen, Germany).

Table 1: The physical properties of different grades of lactose.

Type	Crystallinity* (%)	Particle size** (μm)	Morphology	Bulk density (g/cm^3)	Solubility
α-Lactose monohydrate 90M	100	135	non-granular	0.76	1 in 5
α-Lactose monohydrate 100M	100	130	non-granular	0.75	1 in 5
α-Lactose monohydrate 200M	100	40	non-granular	0.55	1 in 5
α-Lactose monohydrate 450M	100	20	non-granular	0.47	1 in 5
Anhydrous β-lactose	100	150	granular	0.67	1 in 2.2
Spray dried lactose	80-85	110	granular	0.61	Unknown

**Sieve diameter (certificate of analysis, DMV)
* Crystalline fraction

9.3 Methods

9.3.1 Single-step granulation/tabletting

Single-step granulation/tabletting was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1, equipped with a standard screw profile and a circular 9 mm die attached to the extruder outlet. Processing parameters were set at 25°C barrel temperature, 250 rpm screw speed, 5.6 kg/h total input rate and 11.5 and 9.5% water concentration for formulations without and with 2.5% PVP, respectively. These parameters are the optimal processing parameters for α-lactose monohydrate 200M (Keleb et al. 2001). Each formulation was processed at these reference conditions. If the process blocked (for formulations without PVP) or discontinuous extrudate flow (for formulations containing PVP) was observed, further process optimisation was performed.

The granulation liquid (pure water or an aqueous PVP solution) was pumped into the extruder barrel using a peristaltic pump (Watson Marlow, Cornwall, UK). All water concentrations mentioned are based on the wet extruded mass, while the PVP concentration is based on dry weight. Immediately after extrusion, tablets (thickness: 4 mm) were manually cut using surgical blades (Keleb et al. 2001). The tablets were oven-dried at 25°C for 20 h.

9.3.2 High shear granulation and tabletting

Formulations successfully processed by single-step granulation/tabletting were also processed by high shear granulation. The high shear granulation process was performed in a Gral 10 (Machines Collette, Wommelgem, Belgium) (capacity of high shear mixer: 8 l) at 500 rpm impeller speed, 3000 rpm chopper speed, a total load of 0.16 $kg.l^{-1}$ and 10% water concentration. These parameters are the optimal granulation parameters of α-lactose monohydrate 200M (Keleb et al. 2002; Ameye et al., 2002). After a 2 min mixing period of the powder, the required amount of granulation liquid (pure water or an aqueous 2.5% PVP solution) was continuously added over a period of 10 min using a peristaltic pump (Watson Marlow, Cornwall, UK). Wet massing was continued for 2 min following complete liquid addition. All water concentrations mentioned are based on the wet extruded mass, while PVP concentration is based on dry weight.

The granules ($F_{250\text{-}710\ \mu m}$) were blended with 0.5% (w/w) magnesium stearate (<90 μm) (BUFA, Brussels, Belgium) in a Turbula mixer (Bachofen, Basel, Switzerland) for 1 min. Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN per tablet. Similarly, tablets were prepared with die lubrication using magnesium stearate solution (1%, w/v) in ethanol.

9.3.3 Tablet evaluation

The same methods as described in Chapter 3 were used to determine the friability, tensile strength and disintegration of the tablets. The porosity of the tablets was determined as described in Chapter 4.

9.3.4 Tablet stability

α-Lactose monohydrate tablets without and with 2.5% PVP prepared by single-step granulation/tabletting, were stored at 60% RH – 25°C and 75% RH – 40°C for one year. The tablets were evaluated for tensile strength, friability and disintegration time after 1, 90, 180 and 360 days.

9.4 Statistical analysis

The influence of lactose grades, production technique and storage on tablet tensile strength and disintegration time was determined using one-way ANOVA. To further compare the influence of those factors on the tablet properties a multiple comparison among pairs of means of tensile strength and disintegration time was performed using Scheffé test with $P < 0.05$ as a significance level. The data were first tested for normality with a Kolmogorov-Smirnov test and for homogeneity of the variances with a Levene's test. Statistical analysis was performed using the computer program SPSS version 11.0.

9.5 Results and discussion

The influence of lactose particle size on the feasibility of single-step granulation/tabletting and on the properties of the tablets was investigated by comparing α-lactose monohydrate 450M, 200M, 100M and 90M. The influence of lactose morphology and crystallinity was investigated by comparing anhydrous β-lactose, spray dried lactose and α-lactose monohydrate 90M, which have a similar particle size but different particle morphology and crystallinity.

9.5.1 Influence of the particle properties on single-step granulation/tabletting process.

9.5.1.1 Influence on powder feeding

Although α-lactose monohydrate 200M was easily fed from the feed hopper towards the extrusion barrel using a double screw feeder, the other lactose grades exhibited problems during feeding. α-Lactose monohydrate 100M and 90M induced too much friction resulting in a gradual decrease in feeding rate and difficulties in the screw rotation or even blocking of the screw movement. α-Lactose monohydrate 450M tended to stick at the hopper surface during feeding, mainly due to the cohesiveness of the powder leading to feeding inconsistencies. Powder feeding of anhydrous β-lactose exhibited similar problems as α-lactose monohydrate 90M. However, spray dried lactose, which has a similar particle size but different shape (round particles) was reproducibly fed into the extruder barrel. These results indicated that not only particle size but also particle morphology affected feeding by the double screw feeder. These observations clearly indicated the need of the use of a suitable feeding system.

9.5.1.2 Influence on the total input rate

To perform single-step granulation/tabletting adequate pressure at the die block is required to push the wet plastic mass through the die. For formulations without PVP sufficient pressure is required to avoid die blocking (probably due to drying of the extrudates in the die). For formulations with PVP a sufficient pressure is required to ensure good shape and continuous flow of the extrudates. The required pressure is only obtained at a certain degree of screw filling, which depends on the material properties. For instance, a total input rate of 5.6 kg/h used previously for α-lactose

monohydrate 200M (Keleb et al. 2001) was too low for α-lactose monohydrate 100M and 90M, which required a total input rate of at least 6.5 kg/h. On the other hand for α-lactose monohydrate 450M the process was only possible at a total input rate of 4.5 kg/h. Anhydrous β-lactose and spray dried lactose had a lower optimal total input rate (5.6 kg/h) when compared with α-lactose monohydrate 90M. This indicated that particle size and particle morphology of lactose affected the total input rate and thus the capacity of the process.

9.5.1.3 Influence on the optimal water concentration

Water concentration during extrusion has a great influence on the extrudability (Keleb et al., 2002; Kleinebudde and Lindner 1993). At concentrations above the optimum level the mass became oversaturated and the resulting extrudates were difficult to manipulate, while concentrations just below the optimum yielded dry extrudates which were difficult to cut. A further reduction of the water concentration blocked the process due to the high viscosity of the wet mass.

For formulations without PVP, the extrudability during single-step granulation/tabletting was highly influenced by the size of lactose particles as shown in Table 2. Without PVP, it was only possible to process α-lactose monohydrate 200M at the reference screw speed. Other grades of lactose were difficult to process even at a higher water concentration due to improper viscosity and elasticity. Possibly the residence time at the reference screw speed is to short to produce a mixture with suitable properties to be extruded.

Addition of 2.5% PVP allowed single-step granulation/tabletting of all lactose grades studied. Comparison of the optimal water concentration during the process revealed that this was affected by the particle size. Decreasing lactose particle size resulted in a increasing the water concentration required for single-step granulation/tabletting.

9.5.2 Influence of particle properties on the tablet properties

Without PVP, single-step granulation/tabletting was only feasible for α-lactose monohydrate 200M. These tablets exhibited a tensile strength of 1.0 MPa, a friability of 0.74% and a disintegration time of 36 s. Compared to single step granulation/tabletting α-lactose monohydrate 200M tablets without PVP produced by

Table 2: Process evaluation parameters obtained during single-step granulation/tabletting of different lactose grades.

Process parameters			Process evaluation parameters		Remarks
Input	**Water**	**PVP**	**Temperature**	**Power consumption**	
(kg/h)	*(%)*	*(%)*	*(°C)*	*(%)*	
α-Lactose monohydrate 90M					
5.6	11.5	0			Process blocked due to die blocking
6.5	11.5	0			Process blocked due to die blocking
6.5	13.5	0			Wet extrudates
5.6	9.5	2.5			Discontinuous extrudates flow
6.5	9.5	2.5	40	51	
α-Lactose monohydrate 100M					
5.6	11.5	0			Process blocked due to die blocking
6.5	11.5	0			Process blocked due to die blocking
6.5	13.5	0			Process blocked due to die blocking
5.6	9.5	2.5			Discontinuous extrudates flow
6.5	9.5	2.5	40	23	
α-Lactose monohydrate 200M					
5.6	11.5	0	33	23	
5.6	9.5	2.5	36	25	
α-Lactose monohydrate 450M					
5.6	11.5	0			Process blocked due to die blocking
4.5	11.5	0			Process blocked due to die blocking
4.5	15.5	0			Wet extrudates
5.6	9.5	2.5			Powder accumulated at inlet
4.5	9.5	2.5			Dry extrudates
4.5	10.5	2.5	45	27	
Anhydrous β-lactose					
5.6	11.5	0			Process blocked due to die blocking
5.6	15.5	0			Process blocked due to die blocking
5.6	20.0	0			Wet extrudates
5.6	9.5	2.5			Process stopped due to hard screw moveme
5.6	10.5	2.5	36	31	
Spray dried lactose					
5.6	11.5	0			Process blocked due to die blocking
5.6	13.5	0			Process blocked due to die blocking
5.6	9.5	2.5	36	39	

compression after high shear granulation exhibited a significantly lower tensile strength (0.67 and 0.71 MPa for tablets produced with 0.5% magnesium stearate and with die lubrication, respectively) and a higher friability (1.67 and 1.74%, respectively). However, a significantly higher disintegration time (83 s) was only obtained for tablets produced with 0.5% magnesium stearate.

Fig. 1a shows the tensile strength of tablets with 2.5% PVP obtained by single-step-granulation/tabletting and by compression (after blending with magnesium stearate and after die lubrication) after high shear granulation. For tablets prepared by single step granulation/tabletting lactose particle size and particle morphology did not significantly affect tensile strength and it was always higher than 1 MPa. Comparing the lactose tablets with 2.5% PVP and produced by both techniques revealed that single-step granulation/tabletting resulted in a significantly higher tensile strength for all formulations.

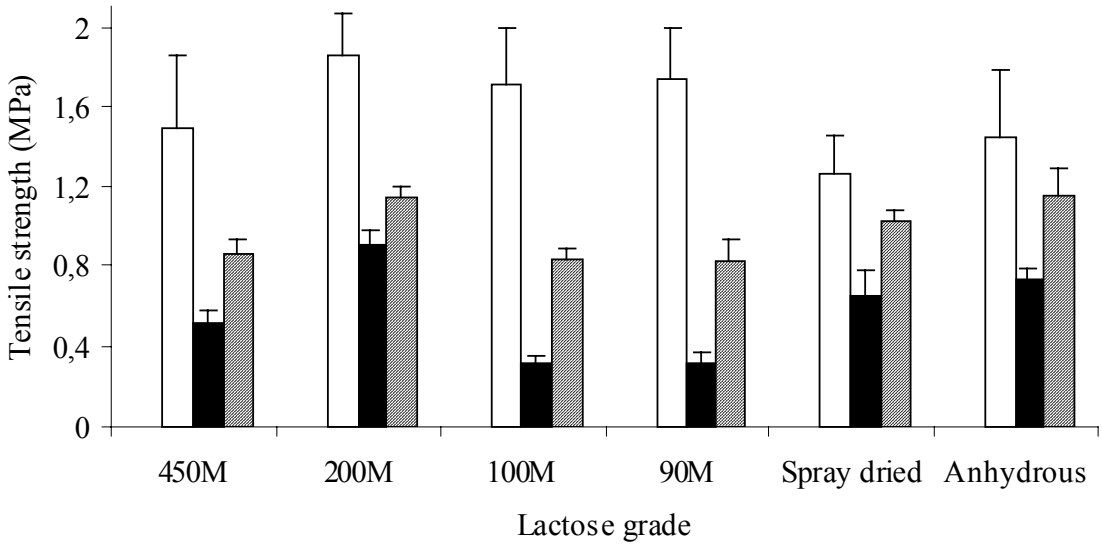

Figure 1a: Tensile strength of tablets (mean ± standard deviation) produced with different grades of lactose with 2.5% PVP produced by single-step granulation/tabletting (□) and by compression after high shear granulation with magnesium stearate (■) and with die lubrication (▨).

The friability was below 1% for all tablets containing PVP, except for α-lactose monohydrate 100M tablets prepared by compression after high shear granulation.

Fig. 1b shows the disintegration time of tablets with 2.5% PVP obtained by single step-granulation/tabletting and by compression after high shear granulation.

All tablets produced by single-step granulation/tabletting had a disintegration time below 400 s. Changing the particle size of α-lactose monohydrate significantly influenced the disintegration time whereas, disintegration of α-lactose monohydrate

90M tablets was significantly slower compared with spray dried lactose and anhydrous β-lactose probably due to solubility differences.

Comparison of tablet disintegration time obtained by both techniques indicated that single-step granulation/tabletting yielded tablets with a significantly lower disintegration time compared with those produced by compression after high shear granulation, except for tablets prepared from α-lactose monohydrate 90M and 200M, which had a similar disintegration time.

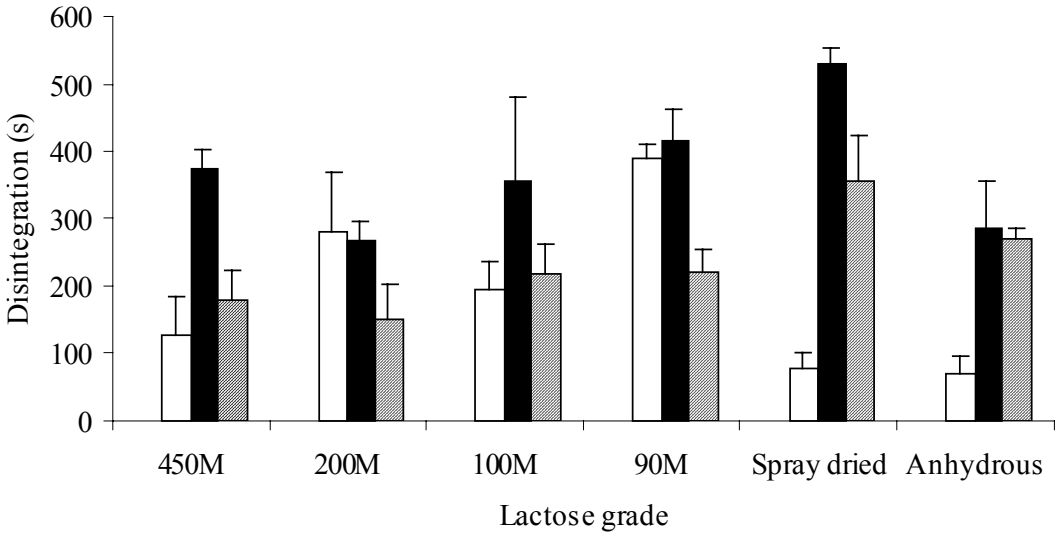

Figure 1b: Disintegration time of tablets (mean ± standard deviation) produced with different grades of lactose with 2.5% PVP produced by single-step granulation/tabletting (□) and by compression after high shear granulation with magnesium stearate (■) and with die lubrication (▨).

9.5.3 Stability of tablets produced by single-step granulation/tabletting

It is well known that the properties of α-lactose monohydrate tablets can be affected by storage (Stubberud et al., 1996) and that this is mainly due to change in the bonding. Tablets obtained by single-step granulation/tabletting are bond mainly by a solid bridges, whereas tablets prepared by compression are bond mainly by intermolecular bonds.

The properties of these tablets could be affected differently during storage according to the type of bonds acting between tablet particles. Therefore, the stability of tablets

Table 3: The influence of long term and accelerated stability conditions on the properties of α-lactose monohydrate tablets without and with 2.5% PVP produced by single-step granulation/tabletting.

		60% RH - 25°C			75% RH - 40°C		
PVP	**Time**	**Tensile strength**	**Friability**	**Disintegration**	**Tensile strength**	**Friability**	**Disintegration**
(%)	*(d)*	*(MPa)*	*(%)*	*(s)*	*(MPa)*	*(%)*	*(s)*
0	1	1.09 (0.17)	0.65	27 (7)	1.07 (0.10)	0.99	42 (12)
	90	1.07 (0.16)	0.58	32 (20)	0.93 (0.25)	0.64	45 (20)
	180	0.97 (0.18)	0.82	53 (13)	0.96 (0.18)	0.84	99 (17)
	360	1.03 (0.15)	0.80	43 (10)	1.10 (0.13)	0.70	125 (49)
2.5	1	1.47 (0.14)	0.42	162 (37)	1.29 (0.31)	0.73	182 (44)
	90	1.60 (0.20)	0.57	193 (42)	0.99 (0.36)	0.79	313 (28)
	180	1.32 (0.22)	0.59	172 (69)	1.34 (0.22)	0.65	223 (92)
	360	1.63 (0.24)	0.90	297 (86)	1.27 (0.14)	0.59	358 (40)

Standard deviations are given between parentheses

of α-lactose monohydrate 200M produced by single-step granulation/tabletting was evaluated during one year storage at 60% RH-25°C and 75% RH-40°C.

Table 3 shows the influence of storage on the properties of tablets without and with 2.5% PVP produced by single-step granulation/tabletting. Storage did not result in significant changes in the tensile strength, while a significant increase in the disintegration time was observed for both formulations at both storage conditions. The disintegration time always remained below 400 s. This is in contrast to Stubberud et al. (1996) who reported that lactose monohydrate tablets prepared by compression hardened during storage and indicate that the effect of storage on the mechanical properties of tablets is dependent on the bonding mechanism.

Comparing the tablet properties obtained at different conditions revealed no significant influence on the tensile strength, while a significantly higher disintegration time was observed for the tablets stored at 75% RH and 40°C. The high disintegration time at 75% RH-40°C could be attributed to a decrease in the tablet porosity from 24.6 to 18.1%. This change in porosity was mainly due to the continuous swelling and transformation of PVP from the glassy state to a rubbery state at elevated humidity and temperature (Kiekens et al., 2000; Fitzpatrik, 2002).

9.6 Conclusion

This study showed that the particle size and morphology of lactose can have a major impact on the performance of single-step granulation/tabletting. However, selection of the proper lactose grade and optimisation of the total input rate as well as PVP and water concentration can easily solve these problems. Tablets of different grades of lactose produced by single-step granulation/tabletting possess better qualities compared to those obtained by compression after high shear granulation.

The stability study revealed that the physical properties of lactose tablets prepared by single-step granulation/tabletting were maintained during storage.

It can be concluded that single-step granulation/tabletting can be applied to different grades of lactose. Moreover, this technique is efficient and allows continuous processing.

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10 Single step granulation/tabletting of highly dosed drugs: a comparison with high shear granulation

Submitted for publication in Drug Dev. Ind. Pharm.

10.1 Introduction

The pharmaceutical industry often faces difficulties in the processing of highly dosed drugs because many active substances have poor compactability or bad flow properties. Using conventional tabletting techniques, suitable excipients are required in order to obtain satisfactory tablets containing such drugs. However, for highly dosed drugs, the percentage of excipient that can be incorporated in the formulation is limited.

For some highly dosed drugs an improved compactability could be obtained by changing the morphology of the drug crystals, but this requires strict process control and can result in the incorporation of impurities in the drug crystals (Garekani et al., 1999; 2000; Abdelillah et al., 1995; Di-Martino e al., 2001).

Recent experiments revealed that single-step granulation/tabletting of α-lactose monohydrate yielded stronger and faster disintegrating tablets compared with those produced by conventional compression.(Keleb et al., 2001). Further investigation of these tablets indicated that their high tensile strength was attributed to a different bonding mechanism, while the faster disintegration was explained by a higher porosity and a larger pore size. This technique might therefore be useful for processing highly dosed drugs.

Paracetamol is a highly dosed, medium water soluble drug possessing a poor compactability and yielding tablets exhibiting a high tendency to cap and laminate. Cimetidine is a highly dosed drug exhibiting good compactability, but poor flow and poor tablet disintegration properties. The aim of this study was to assess the suitability of single-step granulation/tabletting for the production of highly dosed paracetamol and cimetidine tablets and to compare the properties of these tablets with those obtained by compression after high shear granulation. The influence of storage on the stability of paracetamol tablets produced by single-step granulation/tabletting was assessed.

10.2 Materials

α-Lactose monohydrate, with an average particle size of 36 μm, (Pharmatose® 200M) was obtained from DMV (Veghel, The Netherlands), cimetidine, with an average particle size of 61 μm, was purchased from Roig Farma (Barcelona, Spain), paracetamol with an average particle size of 139 μm, was obtained from Mallinckrodt (Capitol Boulevard, NC, USA). Polyvinylpyrrolidone (PVP, Kollidon® K30) and crospovidone (PVP-CL, Kollidon® CL) were received from BASF (Ludwigshafen, Germany).

10.3 Methods

10.3.1 Single-step granulation/tabletting

Single-step granulation/tabletting was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1, equipped with a standard screw profile and a circular 9 mm die attached to the extruder outlet (Keleb et al., 2001). Processing parameters were set at 25°C barrel temperature, 250 rpm screw speed and 5.6 kg/h total input rate (powder and binding liquid). The water concentration was optimised for each formulation. When α-lactose monohydrate or crospovidone was incorporated in the formulation it was preblended with the drug for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). The granulation liquid (pure water or a 2.5% aqueous PVP solution) was pumped into the barrel by means of a peristaltic pump (Watson Marlow, Cornwall, UK). Immediately after extrusion, tablets (thickness: 4 mm) were manually cut using surgical blades (Keleb et al., 2001). The tablets were oven-dried at 25°C for 20 h. All water concentrations were calculated based on the wet mass, while PVP, cimetidine and paracetamol concentrations were calculated based on dry weight.

Single-step granulation/tabletting was characterised by monitoring the following process parameters: die pressure, power consumption and barrel temperature. If the power consumption exceeded 80% of its maximum or the die pressure was above 5 bar the process was stopped in order to avoid machine damage.

10.3.2 High shear granulation and tabletting

High shear granulation was performed in a Gral 10 (Machines Collette, Wommelgem, Belgium). When α-lactose monohydrate or crospovidone was incorporated in the formulation it was blended with the drug for 15 min at 60 rpm in a planetary mixer (Kenwood Major, Hampshire, UK). The granulation process was performed at 500 rpm impeller speed, 3000 rpm chopper speed, a total load of 0.16 $kg.l^{-1}$ and 10% water concentration. After a 2 min mixing period of the powder, the required amount of granulation liquid (water or a 2.5% aqueous PVP solution) was continuously added over a period of 10 min using a peristaltic pump (Watson Marlow, Cornwall, UK). Wet massing was continued for 2 min following complete liquid addition. Granules were oven dried at 25°C for 20 h.

The granules ($F_{250\text{-}710\ \mu m}$) were blended with 0.5% (w/w) magnesium stearate (<90 μm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland) for 1 min. Tablets (250 mg) were prepared using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm at a compression force of 10 kN per tablet.

10.3.3 Tablet evaluation

Tablet friability, tensile strength and disintegration were determined as described in Chapter 3. To determine tablet porosity and in-vitro dissolution the methods described in Chapter 4 were used.

10.4 Tablet stability

Tablets without PVP containing 20% paracetamol and with 2.5% PVP containing 80% paracetamol, prepared by single-step granulation/tabletting, were stored at 60% RH and 25°C and at 75% RH and 40°C for one year. Tablets were evaluated for tensile strength, friability, disintegration and dissolution after 1, 90, 270 and 360 days.

10.5 Statistical analysis

Statistical analysis was performed using the computer program SPSS version 11.0. Statistically significant differences between the tensile strength and disintegration time of tablets produced by single-step granulation/tabletting and by compression after high shear granulation as well as the influence of storage time and storage conditions on tablet tensile strength and disintegration time were determined using a one-way ANOVA. For further comparison of the influence of production technique, storage time and condition on the tablet properties a multiple comparison among pairs of means performed using Scheffé test with $P < 0.05$ as a significance level was used. The data were tested for normal distribution with a Kolmogorov-Smirnov test. The homogeneity of variances was tested with the Levene's test.

10.6 Results and discussion

10.6.1 Process characterization

Table 1 shows the process parameters obtained during preparation of paracetamol and cimetidine tablets by single-step granulation/tabletting. Paracetamol processing without PVP was only possible at a drug load of 20%. Processing of formulations containing 40% paracetamol or more created too much friction inside the extrusion barrel and process blocking within the first few minutes of the process (even at higher water concentrations). Cimetidine processing without PVP was not possible even at a drug load of 20%. The fact that single-step granulation/tabletting of pure cimetidine and paracetamol without PVP was not possible at the set parameters was probably due to their physical properties. Both drugs have lower (1 in 70 for paracetamol and 1 in 88 for cimetidine) water solubility than α-lactose monohydrate 200M (1 in 5), which was easily processed at the same settings. A formulation containing 20% paracetamol could be processed whereas, single-step granulation/tabletting of a mixture containing 20% cimetidine was not feasible. This can be attributed to their different particle size. This is in agreement with previous experiments showing that the feasibility of the single-step granulation/tabletting depends on the particle size (Keleb et al., 2004). Addition of 2.5% PVP improved processing and allowed single-step granulation/tabletting of formulations containing up to 97.5% of both drugs

investigated. Smooth surfaced extrudates were obtained at all concentrations except for 97.5%, which had minor surface roughness. This roughness disappeared on addition of 5% crospovidone.

When processing 97.5% cimetidine, a higher water concentration was required than for the 97.5% paracetamol formulation. This difference could again be attributed to the differences in particle size.

10.6.2 Tablet properties

Fig. 1a shows the tensile strength of paracetamol tablets produced by single-step granulation/tabletting and by compression after high shear granulation. Tablets without PVP containing 20% paracetamol prepared by single-step granulation/tabletting showed an average tensile strength of 0.92 MPa. Although, high shear granulation of formulations without PVP containing more than 20% paracetamol was feasible, no acceptable tablets could be prepared from those granules. For the formulation containing up to 40% paracetamol the tablet tensile strength was below

Table 1: Process parameters during single-step granulation/tabletting of formulations containing paracetamol and cimetidine.

Formulation				Process parameters		
Drug *(%)*	**PVP** *(%)*	**PVP-CL** *(%)*	**Water** *(%)*	**Die Pressure** *(bar)*	**Barrel temperature** *(°C)*	**Power consumption** *(%)*
Paracetamol						
20	0	0	11.5	1	33	22
40	0	0	11.5		Processing not feasible	
100	0	0	11.5		Processing not feasible	
20	2.5	0	9.5	0	33	19
40	2.5	0	9.5	1	33	22
60	2.5	0	9.5	1	31	19
80	2.5	0	10.5	3	30	25
97.5	2.5	0	10.5	3	35	27
92.5	2.5	5	10.5	0	38	30
Cimetidine						
20	0	0	*17.5*		Processing not feasible	
100	0	0	11.5-25.0		Processing not feasible	
80	2.5	0	14.5	0	36	25
97.5	2.5	0	14.5	0	36	34
92.5	2.5	5	14.5	0	33	31

0.60 MPa for tablets prepared with blending with magnesium stearate and with die lubrication. However, no tablets were obtained from granules containing 60% paracetamol due to the tendency for capping and lamination. These data are in agreement with Becker et al. (1997) who reported that paracetamol tablets produced without binder had a poor strength.

Addition of 2.5% PVP to paracetamol formulations resulted in a significant increase in tensile strength for both production techniques. This resulted in hard tablets up to a paracetamol load of 97.5% when prepared by single-step granulation/tabletting. On the contrary, the formulation containing 97.5% paracetamol still showed poor compactability after high shear granulation. Becker et al. (1997) and Symecko et al. (1993) reported similar results and stated that at least 5% binder (e.g. PVP) is required to obtain paracetamol tablets with an adequate tensile strength. The results of tablet tensile strength of both granulation techniques indicated that single step granulation/tabletting resulted in improved tensile strength mainly due to the different bonding mechanism, which come in agreement with data reported by Keleb et al (2004) for different grades of lactose.

Comparison of the tensile strength obtained by both techniques revealed a significantly higher tensile strength for all paracetamol tablets produced by single-step granulation/tabletting.

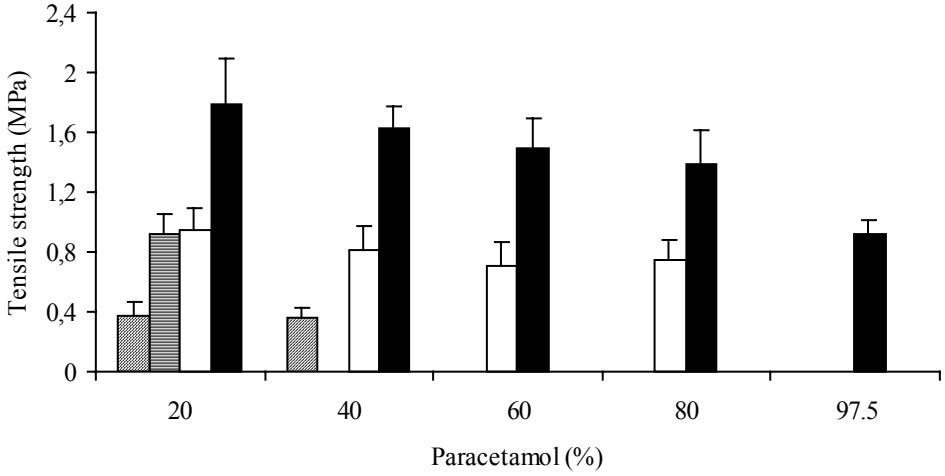


Figure 1a: Tensile strength of paracetamol tablets produced with high shear granulation without PVP (▨) and with 2.5% PVP (□) and by single-step granulation/tabletting without (〓) and with 2.5% PVP (■).

This higher tensile strength can be explained by the different bonding mechanism involved in both techniques. By conventional compression, bonding occurs mainly through intermolecular bonds. Paracetamol exhibits poor compactability due to the weak intermolecular bonds established during compression. In single-step granulation/tabletting bonding occurs mainly through solid bridges formed during drying by resolidification of the material dissolved during the process (Keleb et al, 2001; Vermiere et al., 2004) and these solid bridges are much stronger than intermolecular forces (Nystrom et al., 1993). Evaluation of the effect of paracetamol concentration on tensile strength revealed that only an increase of the paracetamol concentration to 97.5% resulted in a significant decrease of tensile strength. For all formulations the friability of tablets produced by single-step granulation/tabletting ranged between 0.68 and 0.91%, whereas tablet friability was above 1% for all tablets produced by high shear granulation and compression, regardless of the lubrication method employed. The addition of PVP resulted in a considerable reduction of the tablet friability, but did not reduce the friability below 1%.

Fig. 1b shows the disintegration time of paracetamol tablets produced by single-step granulation/tabletting and by compression after high shear granulation. For all paracetamol tablets produced by single-step granulation/tabletting the disintegration time remained below 10 min and was significantly lower than that of tablets made by high shear granulation and compression. This faster disintegration can be attributed to the higher tablet porosity as shown in Fig. 1c. For both production techniques, tablets containing 2.5% PVP showed a significantly higher disintegration time than those without PVP.

For tablets processed by single-step granulation/tabletting increasing the paracetamol concentration resulted in a significantly higher disintegration time only when the drug load was increased to 97.5%, while for tablets produced by high shear granulation and compression the disintegration time increased progressively in function of drug concentration.

For tablets containing more than 20% paracetamol prepared by high shear granulation and compression the addition of PVP resulted in a disintegration time above 15 min.

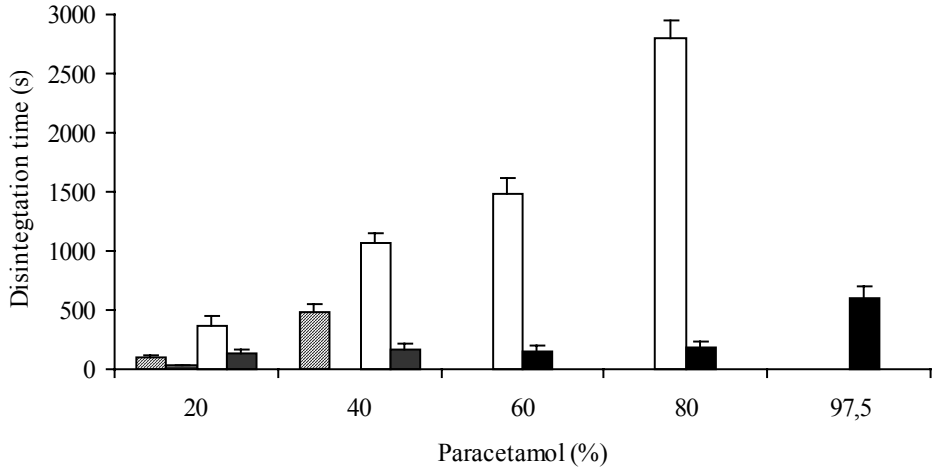


Figure 1b: Disintegration of paracetamol tablets produced by high shear granulation without PVP (▨) and with 2.5% PVP (□) and by single-step granulation/tabletting without PVP (〓) and with 2.5% PVP (■).

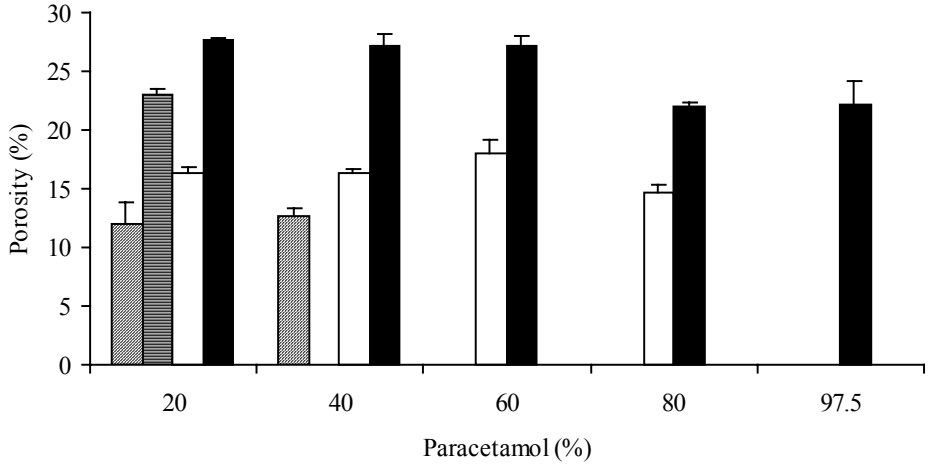


Figure 1c: Porosity of paracetamol tablets produced with high shear granulation without (▨) and with 2.5% PVP (□) and by single-step granulation/tabletting without (〓) and with 2.5% PVP (■).

At increasing paracetamol concentration the fraction of α-lactose monohydrate, (having a 20-fold higher aqueous solubility) decreased and thus the overall solubility of the formulation decreased. This decrease in solubility clearly affected the disintegration time of tablets with low porosity (Fig. 1c) obtained by high shear granulation and compression. The fact that this did not affect the disintegration time of tablets produced by single-step granulation/tabletting indicated that the higher porosity allowed to compensate for the differences in solubility.

Results of the dissolution testing of paracetamol tablets are shown in Fig. 2a and b. Evaluation of the dissolution profiles revealed that tablets prepared by single-step granulation/tabletting exhibited faster dissolution. As for the disintegration, this faster dissolution can be explained by the higher porosity of tablets produced by single-step granulation/tabletting. Tablets produced by single-step granulation/tabletting complied with the USP requirements up to a drug load of 80%, while tablets produced by compression after high shear granulation did only comply up to a drug load of 40%.

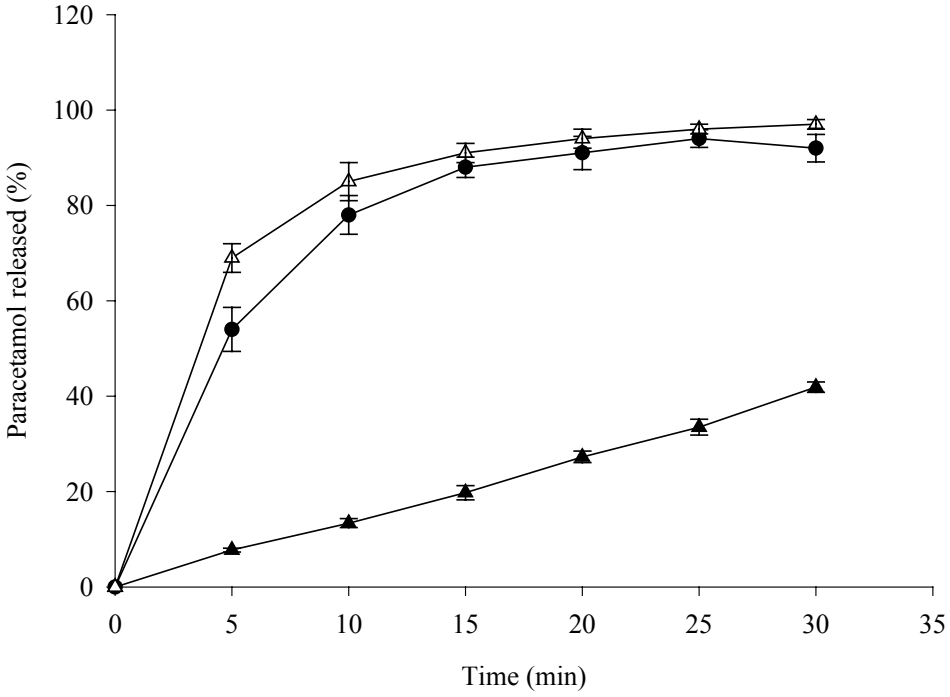


Figure 2a: Dissolution profiles of tablets with 2.5% PVP containing 80% (●), 97.5% (▲) paracetamol and 92.5% paracetamol with 5% crospovidone (△) prepared by single-step granulation/tabletting process.

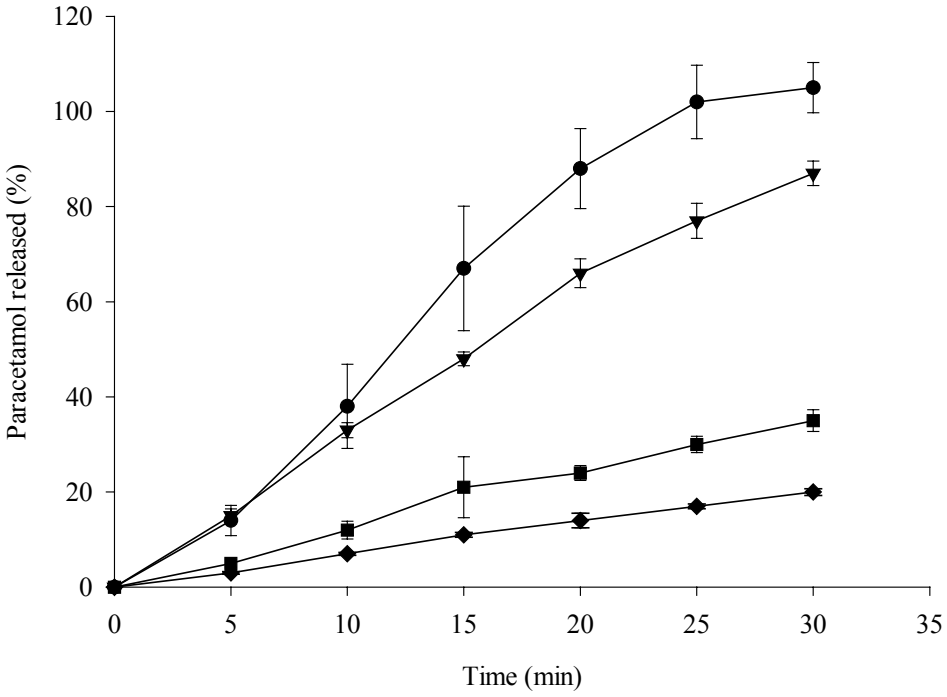


Figure 2b: Dissolution profiles of tablets containing 20% (●), 40% (▼), 60% (■) and 80% (♦)paracetamol prepared by compression after high shear granulation.

Evaluation of the different tablet properties shows that by compression, no acceptable tablets could be obtained without PVP and acceptable tablets were only obtained with 2.5% PVP up to 40% paracetamol. This clearly showed that for formulations with poor compaction properties single-step granulation/tabletting allowed to manufacture quality tablets, whereas conventional high shear granulation and tabletting failed. The potential of the single-step granulation/tabletting process for producing tablets of formulations with poor disintegration and flow properties was assessed using cimetidine as a model drug.

Fig. 3a, b and c show the tensile strength, the disintegration time and the porosity of cimetidine tablets produced by single-step granulation/tabletting and by compression after high shear granulation. Tablets containing 97.5% cimetidine and 2.5% PVP produced by single-step granulation/tabletting showed a significantly lower tensile strength (0.85 MPa), a significantly lower disintegration time (< 15 min), lower friability (0.93%) and faster dissolution than those produced by high shear granulation

and compression (with blending with magnesium stearate). Similarly single step granulation/tabletting showed a significantly lower tensile strength and lower disintegration time than tablets produced after high shear granulation and compression with die lubrication (data not shown). These results indicated that the improved disintegration for tablets produced by single step granulation/tabletting is mainly due to the higher porosity.

Although single-step granulation/tabletting resulted in an improved disintegration time of cimetidine tablets mainly due to the higher porosity (Fig. 3c), incorporation of 17.5% α-lactose monohydrate 200M in the cimetidine formulation with PVP yielded tablets with a significantly lower disintegration time (198 s), a significantly lower tensile strength (1.30 MPa) and faster dissolution than those produced by high shear granulation and compression. The dissolution profile of these cimetidine tablets with 17.5% α-lactose monohydrate complied with the pharmacopoeial requirements (Fig. 4). In another attempt to improve the disintegration and dissolution of pure cimetidine tablets, 5% crospovidone was added. This resulted in a disintegration time below 3 min (Fig. 3b). The tablets produced by both techniques complied with the USP requirements (not less than 75% of the labelled amount dissolved in 15 min) (Fig. 4).

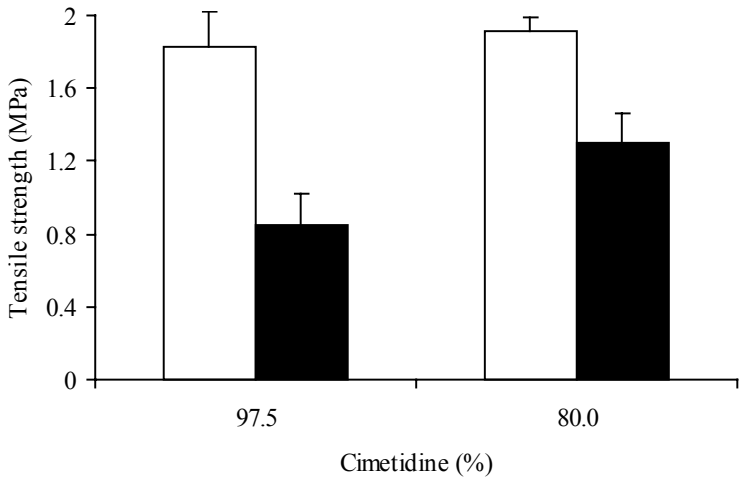


Figure 3a: Tensile strength of cimetidine tablets containing 2.5% PVP produced by high shear granulation (□) and by single-step granulation/tabletting (■)

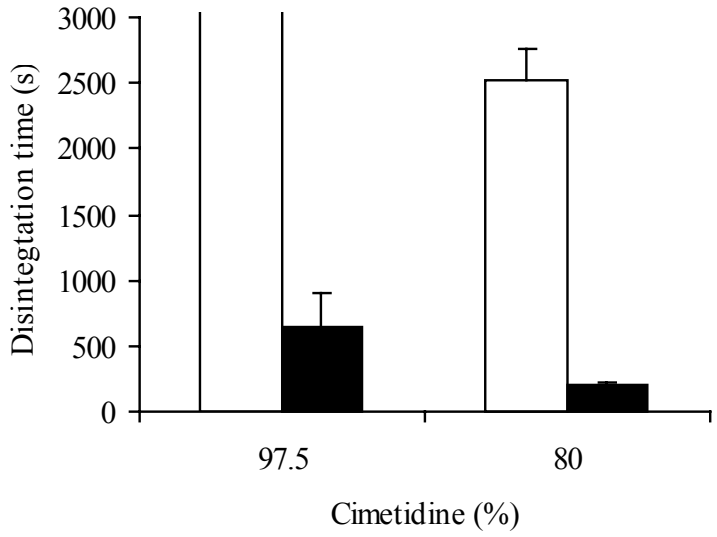


Figure 3b: Disintegration time of cimetidine tablets containing 2.5% PVP produced by high shear granulation (□) and by single-step granulation/tabletting (■).

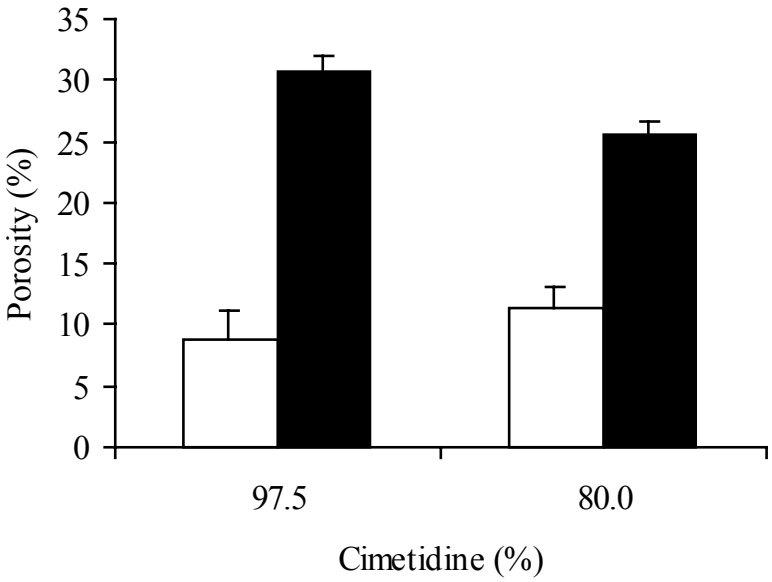


Figure 3c: Porosity of cimetidine tablets containing 2.5% PVP produced by high shear granulation (□) and by single-step granulation/tabletting (■).

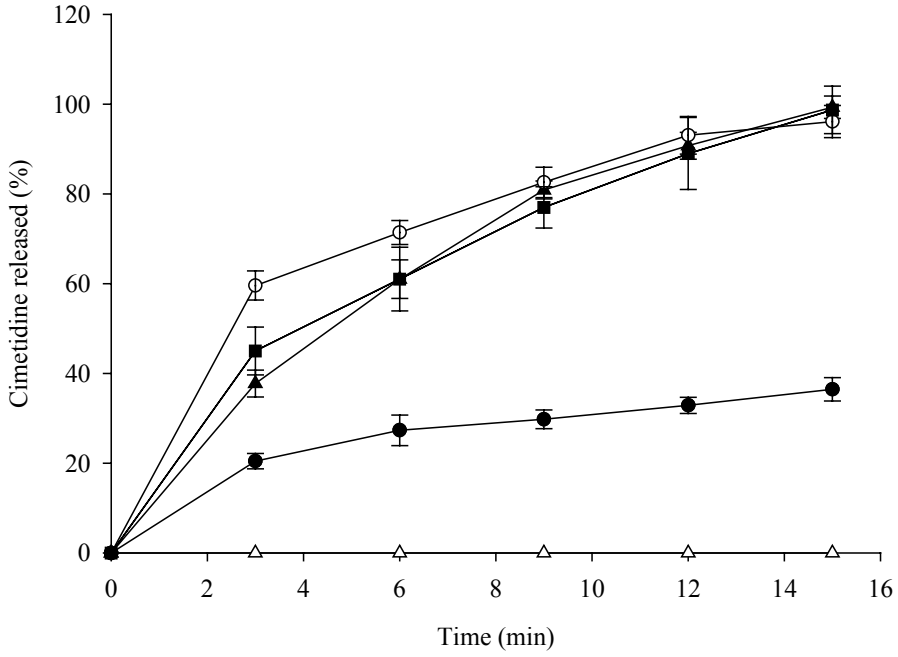


Figure 4: Dissolution profiles of cimetidine tablets with 2.5% PVP produced by single-step granulation/tabletting containing 97.5% (●), 92.5% + 5% crospovidone (O), 80% + 17.5% α-lactose monohydrate 200M (■) and by compression after high shear granulation containing 97.5% (△) and 92.5% cimetidine + 5% crospovidone (▲).

10.6.3 Stability of paracetamol tablets produced by single-step granulation/tabletting

As it is known that tablet properties can be affected by storage conditions, the stability of tablets produced by single-step granulation/tabletting was evaluated during one year storage at 60% RH-25°C and 75% RH-40°C. This stability study was performed on tablets without PVP containing 20% paracetamol and with 2.5% PVP containing 80% paracetamol.

Table 2 shows the influence of storage on the properties of those tablets. It is obvious that storage had no significant influence on the tensile strength, but resulted in a significant increase in the disintegration time for both formulations studied. However, the disintegration time remained below 5 min. The increase in disintegration time could be explained by a minor decrease in the tablet porosity. Additional porosity measurements after one year revealed that storage of tablets at 75% RH–40°C resulted

in a reduction of the porosity from 23 and 22% to 18.7 (± 0.85) and 19.3% (± 0.73) for formulations containing 20 and 80% paraceatmol, respectively. However, no influence on the tablet porosity was observed for tablets stored at 60% RH–25°C. For both formulations no change in dissolution profile was observed over a period of one year as shown in Fig. 5.

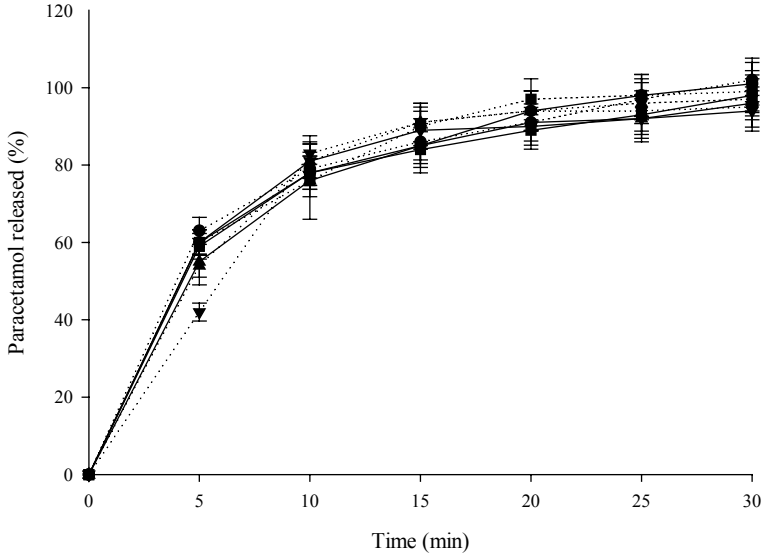
It is clear that paracetamol tablets produced by single step-granulation/tabletting were not influenced by the storage conditions. After a storage period of one year, these tablets had a high tensile strength, fast disintegration time and a dissolution profile that complied with the pharmacopoeial requirements. Whereas, paracetamol tablets produced by compression after wet granulation exhibited a significant increase in the tablet tensile strength and disintegration time and a slower dissolution after storage, even though they contained disintegrant (Khatab et al., 1993; Sarisuta and Parrot, 1988).

Table 2: The influence of storage on the properties of tablets (without PVP) containing 20% paracetamol and tablets (with 2.5% PVP) containing 80% paracetamol produced by single-step granulation/tabletting.

			60% RH - 25°C			75% RH - 40°C		
Time *(d)*	**Paracetamol** *(%)*	**PVP** *(%)*	**Tensile strength** *(MPa)*	**Friability** *(%)*	**Disintegration** *(s)*	**Tensile strength** *(MPa)*	**Friability** *(%)*	**Disintegration** *(s)*
1	20	0	0.84 (0.19)	0.44	32 (6)	0.88 (0.12)	0.84	36 (8)
60			0.76 (0.11)	0.68	39 (5)	1.07 (0.14)	0.66	72 (29)
180			0.81 (0.19)	0.83	33 (17)	0.98 (0.25)	0.68	86 (19)[a]
360			0.88 (0.20)	0.88	70 (15)[a]	0.95 (0.18)	0.68	119 (20)[a]
1	80	2.5	1.39 (0.21)	0.99	112 (23)	1.24 (0.11)	1.02	91 (18)
60			1.40 (0.27)	0.95	109 (23)	1.37 (0.32)	0.75	121 (23)
180			1.43 (0.21)	0.72	130 (31)	1.42 (0.22)	0.97	173 (25)
360			1.50 (0.47)	0.97	201 (31)[a]	1.27 (0.37)	0.83	210 (48)[a]

[a] Significantly different from the other values in the same group.
Standard deviations are given between parentheses

a



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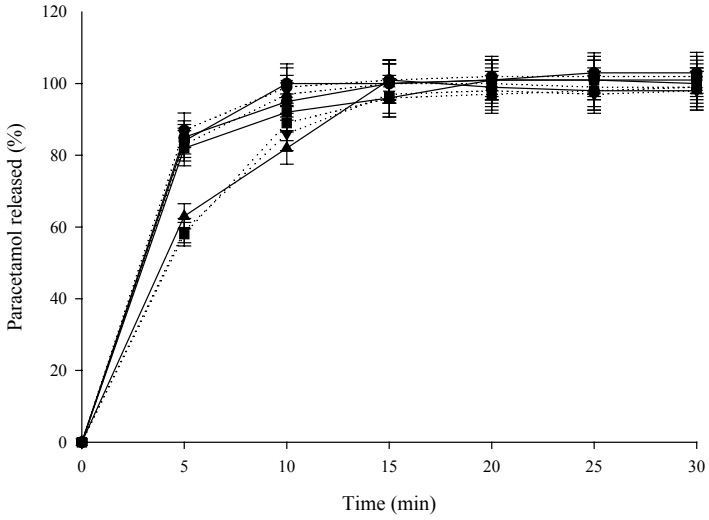

Figure 5: Dissolution profiles of (a) tablets containing 20% paracetamol without PVP and (b) tablets with 2.5% PVP containing 80% paracetamol prepared by single-step granulation/tabletting after storage for 1 (●), 90 (■), 270 (▲), and 360 days (—) at 60% RH–25°C (·····) and at 75% RH– 40°C (▼), respectively

10.7 Conclusion

From these experiments it can be concluded that single-step granulation/tabletting allowed to produce acceptable tablets at a higher drug level than conventional high shear granulation and compression. Single-step granulation/tabletting allows to produce paracetamol and cimetidine tablets with acceptable tensile strength, fast disintegration time and dissolution profile that complied with the pharmacopoeial requirements up to a drug load of 80%. However, addition of PVP and incorporation of 5% crospovidone allowed to produce tablets containing 92.5% paracetamol or cimetidine that complied with the pharmacopoeial requirements.

The paracetamol tablets and the cimetidine tablets produced by single-step granulation/tabletting exhibited a higher tensile strength and faster disintegration compared with tablets produced by compression after high shear granulation. Paracetamol tablets produced by single-step granulation/tabletting were not influenced by the storage conditions investigated over a period of one year.

It can be concluded that single-step granulation/tabletting is an efficient tool for the preparation of tablets of highly dosed drugs and can significantly improve their tablet properties.

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11 Physical stability of tablets: a comparison between single step granulation/tabletting and compression

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11.1 Introduction

Physical tablet properties may be altered during storage, the effect of storage depending on the physical properties of the raw materials (crystallinity, solubility, etc.), the manufacturing process and the storage conditions (time, relative humidity and temperature). The most commonly occurring physical changes are tablet hardening and softening. These changes are suggested to be due to changes in the bonding between particles. Tablet hardening is mainly attributed to the formation of solid bridges between particles or an increase in the bonding surface area, while tablet softening is mainly due to the disruption of the bonds formed during compaction (e.g. transition of amorphous molecules from a glassy state to a rubbery state). As these phenomena are not always reversible tablet properties not only depend on the actual storage conditions, but can be dramatically affected by prior storage (Riepma et al., 1992; Alderborn and Ahlneck, 1991; Kiekens et al., 2000; Stubberud et al., 1996a and b).

Continuous single-step granulation/tabletting was reported to be a promising and robust technique, yielding good quality tablets for formulations with poor compactibility or disintegration properties (Keleb et al., 2001, 2004). These tablet properties were explained by a different mechanism of tablet formation, i.e. by solid bridges rather than by short distance forces as in compressed tablets (Vermeire et al., 2004). As modifications at the bonding sites induce physical changes, the physical stability of tablets prepared by both techniques (single-step granulation/tabletting vs. compression) might be different. Because solid bridges are the dominating bonding mechanism in tablets prepared by single-step granulation/tabletting, these tablets might not harden on storage. Moreover, single-step granulation/tabletting yields tablets with a different internal structure, and are possibly differently affected by glass-to-rubber transitions of amorphous material. The effect of storage conditions on lactose compacts and lactose/PVP compacts has been studied previously. From these studies it was clear that α-lactose monohydrate tablets can harden on storage and that transferring the tablets from a high to a low relative humidity environment caused a dramatic increase in tensile strength. These changes were attributed to the formation of solid bridges (Riepma et al., 1992; Stubberud et al., 1996). The presence of PVP was reported to weaken the compacts

when stored at high relative humidity. Because of the glass-to-rubber transition of amorphous PVP (Stubberud et al., 1996).

The aim of the present study was to investigate the influence of storage conditions on the physical stability of α-lactose monohydrate tablets prepared by single-step granulation/tabletting. To evaluate whether the behaviour during storage could be related to the bonding mechanism, tablets manufactured by conventional compression were evaluated in parallel.

11.2 Materials

α-Lactose monohydrate (Pharmatose® 200M) was used as the excipient (DMV, Veghel, The Netherlands) and polyvinylpyrrolidone (PVP, Kollidon® K30, BASF, Ludwigshafen, Germany) as a binder.

11.3 Methods

11.3.1 Preparation of tablets

α-Lactose monohydrate tablets without and with 2.5% (w/w) PVP were prepared by single-step granulation/tabletting, by extrusion/granulation + compression, by high shear granulation + compression and by direct compression.

Extrusion/granulation and single-step granulation/tabletting were performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder (APV Baker, Newcastle-under-Lyme, UK) having a length - to - diameter ratio of 25/1 and equipped with a standard screw profile with two mixing sections and a die block. The α-lactose monohydrate powder and the granulation liquid (pure water or an aqueous PVP solution) were fed into the first zone of the extruder barrel. The powder was fed on top of the screws using a screw operated feeder, while the liquid was pumped into the extruder barrel by means of a peristaltic pump (Watson Marlow, Cornwall, UK). The extrudates were collected 10 min after the process was started in order to allow the system to equilibrate. During processing the extruder was set at a constant temperature (25°C) and the powder volume in the feed hopper was maintained at a constant level (85 – 100% of the total feeder capacity).

For the single-step granulation/tabletting process a 9 mm die was attached to the extruder outlet. Processing parameters were: a screw speed of 250 rpm, a total input rate (powder feed

rate + liquid feed rate) of 5.6 $kg.h^{-1}$ and a water concentration during extrusion of 11.5 and 9.5% (w/w) for the formulation without and with PVP, respectively. Immediately after extrusion, tablets (thickness: 4 mm) were manually cut using surgical blades and oven-dried for 20 h at 25°C (Keleb et al., 2001).

Extrusion/granulation was performed at a screw speed of 250 rpm, a total input rate of 5.6 $kg.h^{-1}$ and a water concentration during extrusion of 7.5% (w/w). Immediately after extrusion the extrudates (400 g) were wet sized using a 1 mm oscillating sieve (Frewitt, Fribourg, Switzerland), operated at a minimal distance between rotor and sieve, and were oven-dried for 20 h at 25°C (Keleb et al., 2002). Prior to compression, the granules ($F_{250\text{-}710\mu m}$) were blended with 0.5% (w/w) magnesium stearate (<90 µm) (BUFA, Brussels, Belgium) in a Turbula mixer (W.A. Bachofen, Basel, Switzerland) for 1 min. Granules were compressed into tablets (250 mg) using an eccentric compression machine (Korsch EKO, Berlin, Germany) equipped with a flat faced double punch of 9 mm diameter at a compression force of 154 MPa.

High shear granulation was performed in a Gral 10 (Machines Collette, Wommelgem, Belgium) at an impeller speed of 500 rpm, a chopper speed of 3000 rpm, a total load of 0.16 $kg.l^{-1}$ and a water concentration of 10% (w/w). After mixing the powder for 2 min, the required amount of granulation liquid (water or an aqueous PVP solution) was continuously added over a period of 10 min using a peristaltic pump (Watson Marlow, Cornwall, UK). Wet massing was continued for 2 min following complete liquid addition. The granules were oven-dried for 20 h at 25°C. Tablets were prepared from these granules as described above.

Tablets were also prepared by direct compression. Formulations with PVP could not be evaluated as tablets with a too low tensile strength were obtained. α-Lactose monohydrate was mixed with magnesium stearate and compressed as described above for the granules.

11.3.2 Storage conditions of tablets

The effect of relative humidity (RH) and temperature during short and long term storage on the tablet properties was studied.

11.3.2.1 Short term storage

α-Lactose monohydrate tablets (n=30), produced by single-step granulation/tabletting and by compression of granules made by extrusion/granulation, were stored at 33, 60, 75 and 93% RH (25°C). After 24 hrs the tensile strength of 6 tablets was determined, while the tablets

(n=24) remaining at each RH were evenly distributed for storage at the different RH's. After another 24 hrs of storage the tensile strength of all tablets was determined.

In another experiment α-lactose monohydrate tablets (produced using the different techniques under evaluation) were stored for 10 days (25°C), alternating the storage conditions every 24 hrs between 33 and 75% RH. Tablets prepared by extrusion granulation + compression were also stored for 6 days, alternating the RH every 24 hrs between 33 and 93% (25°C).

The effect of storage temperature was evaluated by storing tablets (produced using the different techniques under evaluation) for 10 days at constant RH (33%), alternating the temperature every 24 hrs between 25 and 40°C.

11.3.2.2 Long term storage

α-Lactose monohydrate tablets (produced by single-step granulation/tabletting and by compression of granules made by extrusion granulation) were stored for one month at 33, 75 and 93% RH (25°C).

In addition α-lactose monohydrate tablets (produced by compression of granules made by extrusion/granulation) were stored for 2 months at 33 and 75% RH, alternating the RH every month between both conditions. During the first month part of the tablets was stored at 33% RH and part at 75% RH. This experiment was performed at 25 and 40°C.

α-Lactose monohydrate tablets (produced by single-step granulation/tabletting and by compression of granules produced by extrusion granulation) were also stored for 15 months at 25°C/60% RH and at 40°C/75% RH. Next the tablets were transferred to 25°C/33% RH for 24 hrs.

11.3.3 Tablet tensile strength

The same method as described in Chapter 3 was used to determine the tensile strength of the tablets.

11.3.4 Differential scanning calorimetry

Samples of 5 mg PVP were stored in aluminium pans at 25°C (33 and 75% RH) and 40°C (33 and 75% RH) for 1 and 7 days. In addition samples were initially stored for 7 days at 33% RH (or 75% RH) and were then transferred to 75% RH (or 33% RH) for 24 hrs. The

samples were analysed in hermetically sealed aluminium pans by modulated differential scanning calorimetry (MDSC 2920, TA Instruments, New Castle, DE, US). The sample was cooled at rate of 10°C/min to –35°C and maintained at –35°C for 5 min. Afterwards the sample was heated to 80°C at a rate of 2°C/min, a modulation amplitude of 0.5°C and a period of 60s. The glass transition temperatures were determined using peak analysis.

11.4 Statistical analysis

Statistically significant differences between the formulations, manufacturing techniques, storage conditions and storage time were determined using ANOVA. The data were tested for normal distribution with a Kolmogorov-Smirnov test. The homogeneity of variances was tested with the Levene's test. To further compare the effects a multiple comparison among pairs of means was performed using a Scheffé test with $P<0.05$ as significance level. For statistical analysis SPSS version 11.0 was used.

11.5 Results and discussion

11.5.1 Physical stability during storage at constant RH and temperature

Table 1 shows the influence of RH during storage on the tensile strength of α-lactose monohydrate tablets (prepared by single-step granulation/tabletting and compression of granules made by extrusion granulation). Comparison (one-way ANOVA) of the tablet tensile strength after storage at different RH revealed that the tensile strength significantly decreased with increasing RH, this effect was more pronounced for the tablets containing PVP as a binder. The decrease in tensile strength for these tablets observed ≥75% RH is due to the glass-to-rubber transition of PVP as confirmed by the glass transition temperature (Tg) of PVP samples stored at different conditions (Table 2). These data show that already after 1 day at ≥75% RH the Tg of PVP was reduced below the storage temperature, inducing a transition of PVP from its rigid glassy state to a mobile rubbery state. A similar reduction of Tg in function of RH was reported by Oksanen and Zografi (1990). The decrease in tensile strength of compacts containing PVP stored at high RH confirmed earlier findings (Kiekens *et al.*, 2000; Stubberud *et al.*, 1996a and b). The decrease in tensile strength of tablets formulated without PVP and prepared by single-step granulation/tabletting at 93% RH could

be explained by moisture absorption of α-lactose monohydrate above 90% RH (Kibbe, 2000, Alderborn and Ahlneck, 1991), moisture weakening the structure of tablets as it dissolves the solids after condensation on internal pore surfaces.

Table 1: Tensile strength (MPa)(mean ± sd, n=6) of α-lactose monohydrate tablets (produced by single-step granulation/tabletting and by compression of granules made by extrusion/granulation) after storage at 33, 75 and 93% RH (25°C).

PVP (%)	Storage time (days)	Tensile strength (MPa)		
		33% R.H.	75% R.H.	93% R.H.
Extrusion granulation + compression				
0	1	0.56 ± 0.09	0.62 ± 0.06	0.50 ± 0.03
	7	0.58 ± 0.05	0.62 ± 0.06	0.45 ± 0.02
	14	0.54 ± 0.10	0.60 ± 0.03	0.46 ± 0.02
	28	0.40 ± 0.14	0.50 ± 0.04	0.48 ± 0.02
2.5	1	0.96 ± 0.15	0.80 ± 0.10	0.46 ± 0.02
	7	1.26 ± 0.20	0.78 ± 0.08	0.42 ± 0.02
	14	1.38 ± 0.11	1.19 ± 0.08	0.39 ± 0.02
	28	1.44 ± 0.13	1.42 ± 0.05	0.41 ± 0.01
Single-step granulation/tabletting				
0	1	0.94 ± 0.15	0.99 ± 0.10	0.75 ± 0.07
	7	1.06 ± 0.12	1.08 ± 0.07	0.85 ± 0.18
	14	0.97 ± 0.14	1.02 ± 0.10	0.72 ± 0.09
	28	1.15 ± 0.27	1.10 ± 0.13	0.79 ± 0.13
2.5	1	1.57 ± 0.18	1.07 ± 0.20	0.37 ± 0.12
	7	1.56 ± 0.17	1.14 ± 0.26	0.29 ± 0.06
	14	1.56 ± 0.24	1.00 ± 0.09	0.33 ± 0.14
	28	1.59 ± 0.12	1.02 ± 0.14	0.18 ± 0.04

Table 2: Glass transition temperature (Tg)(°C) of PVP samples stored at different conditions of relative humidity (RH) and temperature.

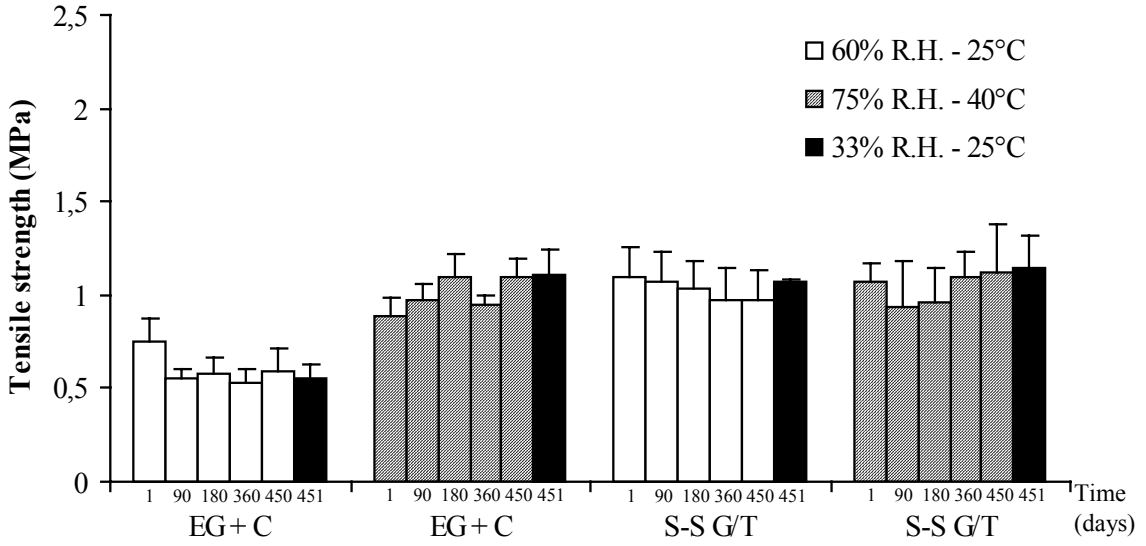
Storage time	Storage conditions			
	25°C/33% RH	25°C/75% RH	40°C/33% RH	40°C/75% RH
1 day	63.2	27.1	57.1	17.8
7 days	59.4	21.0	58.2	23.1
7 days at 75% RH +1 day	57.7		64.2	
1 week at 33% RH +1 day		23.0		22.2

This phenomenon did not affect the tensile strength of compressed tablets as their denser structure allows less moisture to be absorbed. Moreover, in a dense compact dissolution of only a small part of lactose will have less effect on the tablet structure.

The tensile strength remained unchanged during storage for one month at the different conditions, except for the compressed tablets containing PVP as their tensile strength significantly increased during storage at 33 and 75% RH. The gradual increase in tensile strength at 33% RH is probably due to recrystallisation of PVP, thus forming additional solid bridges in the internal tablet structure. The increase in tensile strength at 75% RH could not be due to recrystallisation of PVP as at this RH PVP is expected to weaken the tablets (Table 2). As this increase was not observed during storage of pure α-lactose monohydrate tablets, this increase in tensile strength must be due to a combined effect of α-lactose monohydrate and PVP. As PVP is hygroscopic and will cause more moisture to be absorbed in the compacts (Stubberud et al., 1996a), it is assumed that the higher moisture content in tablets containing PVP allowed partial dissolution and resolidification of α-lactose monohydrate. Besides, the presence of rubbery PVP facilitated rearrangement of solid material at the particle surface area resulting either in the formation of solid bridges or in an increased bonding surface area, two mechanisms contributing to an increase in tensile strength (Alderborn and Ahlneck, 1991). The higher tensile strength of the compressed tablets containing PVP after one month storage at 75% RH in comparison with tablets prepared by single-step granulation/tabletting can be explained by their different internal tablet structure. As compressed tablets are much denser the continuous swelling and recrystallisation of PVP in combination with the migration of rubbery PVP in the compressed tablets probably resulted in numerous solid bridges and hence a higher bonding surface area. Whereas in the porous tablets prepared by single-step granulation/tabletting the weakening effect of the rubbery PVP on the solid bridges predominated.

No change in tensile strength was observed during long term storage independently of the production technique (Fig. 1). This seemed in contradiction with the increase in tensile strength observed for compressed tablets during one month storage at 25°C/75% RH (Table 1). Comparison of the tablet strength at 40°C/75% RH, with the one obtained at 25°C/75% RH revealed that after one day at 40°C a similar tensile strength was obtained as after one month at 25°C. This suggests that the same phenomena occur at both temperatures. At both temperatures the transition of PVP occurred during the first day, as shown by DSC analysis of PVP samples (Table 2).

a.



b

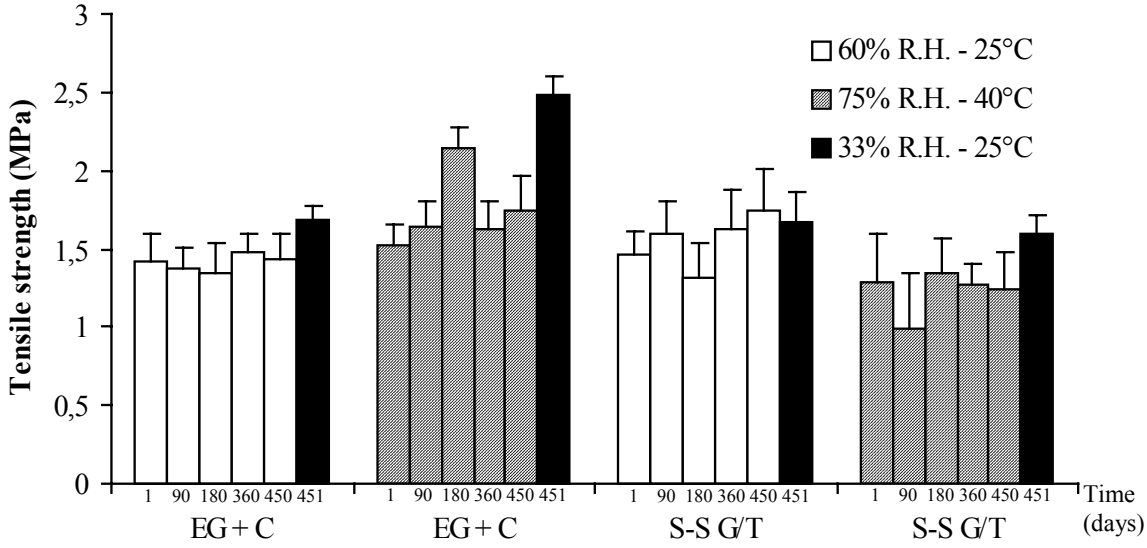


Figure 1: Tensile strength (mean ± sd, n=6) of α-lactose monohydrate tablets, prepared by compression of granules prepared by extrusion/granulation (EG + C) and single-step granulation/tabletting (S-S G/T) after storage for 1 day, 1, 3, 6, 12 and 15 months at 60% RH/25°C and at 75% RH/40°C. After 15 months storage, the tablets were transferred to 33% RH/25°C for 24 hours. (a) tablets without binder, (b) tablets with 2.5% PVP

However, at 40°C the formation of additional solid bridges was already completed within the first day, whereas at 25°C this phenomenon proceeded at a slower rate.

11.5.2 Influence of changing storage conditions

The effect on the physical tablet properties of varying RH during storage was determined during a 2-day storage experiment (Fig. 2): after 24 hrs storage at the initial RH conditions, the tablets were transferred to the final RH and stored for another 24 hrs. Two-way ANOVA of the tensile strength values obtained revealed in all cases a significant ($P<0.001$) interaction between the effect of the initial and the final RH as well as a significant ($P<0.05$) main effect of the initial and the final RH. The effect of the initial RH clearly depended on the manufacturing technique. A lower RH during the second day of storage (final RH) compared with the first day (initial RH) did not affect the tensile strength of tablets prepared by single-step granulation/tabletting, whereas it induced an increase in tensile strength for compressed tablets. For pure α-lactose monohydrate tablets prepared by compression a significant increase in tensile strength was only observed after initial storage at 93% RH. This could be explained by the dissolution of α-lactose monohydrate as described previously. For compressed tablets containing PVP, a significant increase in tensile strength was already observed after initial storage at 75% RH. This increase was larger than for the pure α-lactose monohydrate tablets and was due to the additional effect of the rubber-to-glass transition of PVP, which occurred at ≥ 75% RH. The magnitude of this effect increased with increasing difference between the initial and final RH. Contrary to initial storage at a higher RH, initial storage at a lower RH did not affect the tensile strength, except for PVP-containing tablets prepared by single-step granulation/tabletting where a lower tensile strength was obtained at a RH of 93 % after initial storage at 75% RH. A similar effect, though not significant, was observed for compressed tablets. These results were in agreement with the weakening effect of long term storage at 75% RH (Table 1). The results of this experiment clearly indicated that tablets produced by single-step granulation/tabletting do not harden on storage, even at conditions inducing hardening of the compressed tablets. However, tablet weakening by glass-to-rubber transition is more pronounced in these tablets compared to compressed tablets.

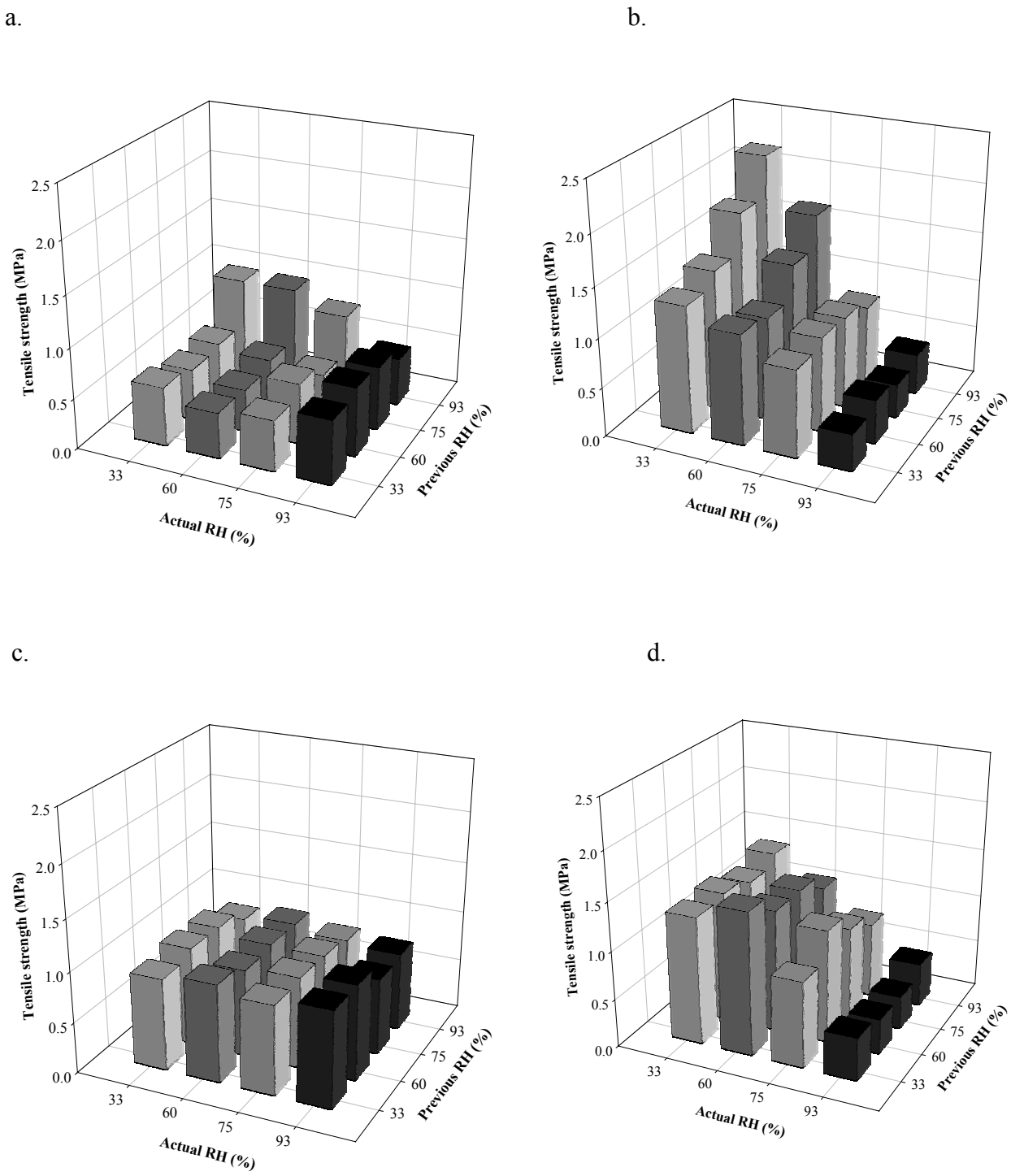
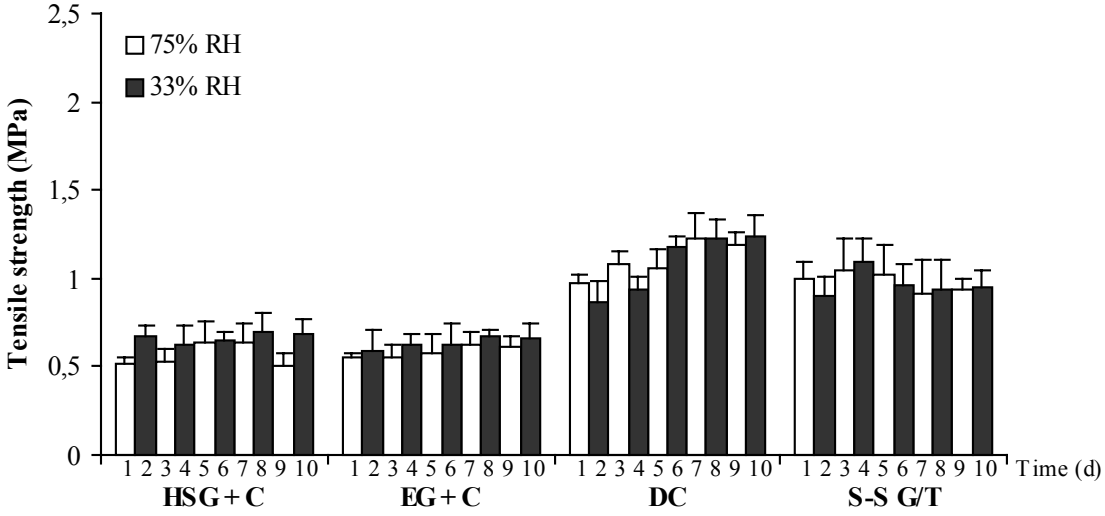


Figure 2: Tensile strength (mean ± sd, n=6) of α-lactose monohydrate tablets, prepared by compression of granules produced by extrusion/granulation (a and b) and single-step granulation/tabletting (c and d). After 24 hrs storage at the initial RH conditions, the tablets were transferred to the final RH and stored for another 24 hrs. (a) and (c) tablets without binder, (b)and (d) tablets with 2.5% PVP.

a.



b.

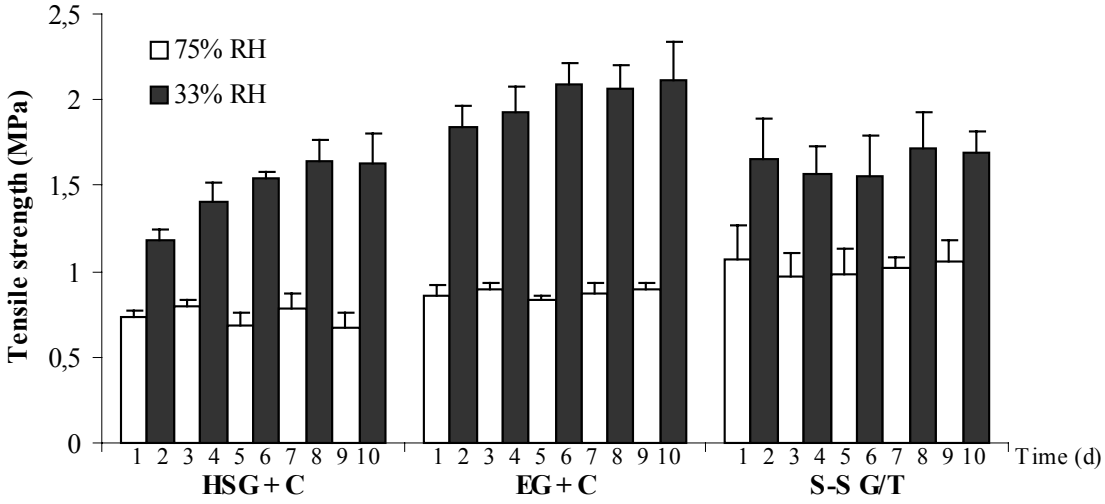


Figure 3: Tensile strength (mean ± sd, n=6) of α-lactose monohydrate tablets, prepared by high shear granulation + compression (HSG + C), extrusion granulation + compression (EG + C), direct compression (DC) and single-step granulation/tabletting (S-S G/T). Tablets were stored (25°C) for 10 days at 33 and 75% RH, alternating the RH every 24 hrs between both conditions. (a) tablets without binder, (b) tablets with 2.5% PVP.

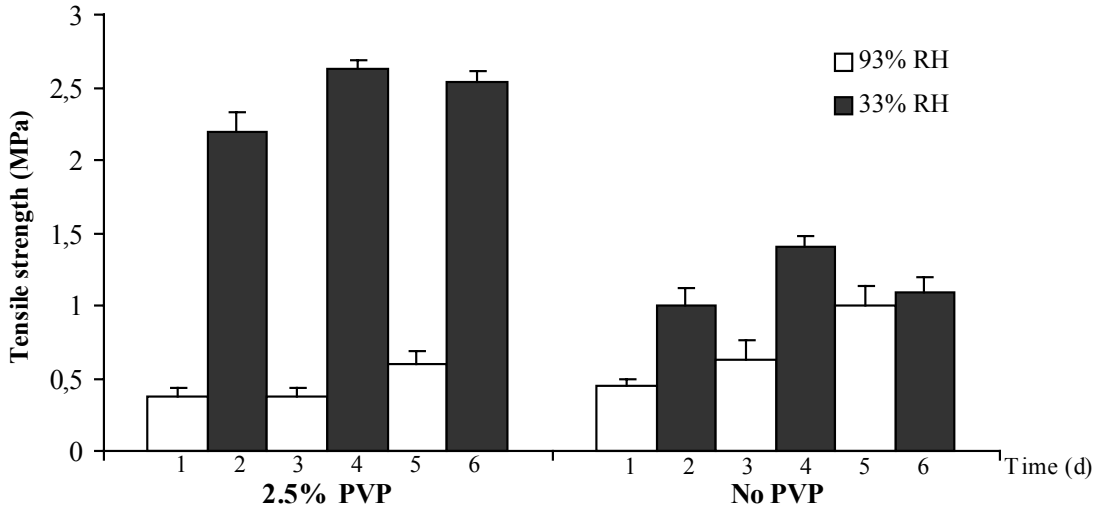
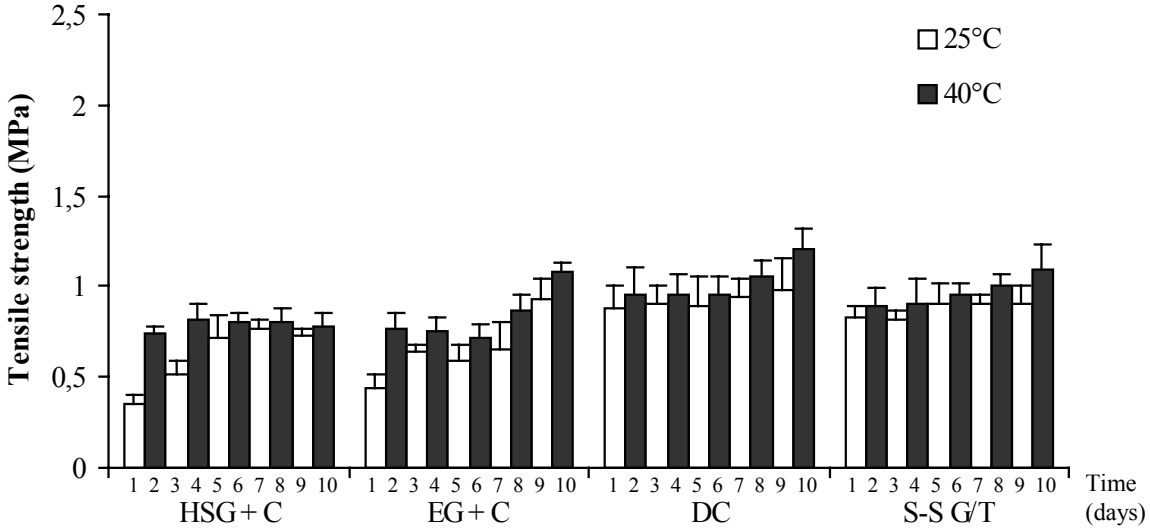


Figure 4: Tensile strength (mean ± sd, n=6) of α-lactose monohydrate tablets without and with 2.5% PVP, prepared by compression of granules prepared by extrusion/granulation. Tablets were stored (25°C) for 6 days at 33 and 93% RH, alternating the RH every 24 hrs between both conditions.

To determine whether these phenomena were reversible tablets were transferred to different storage conditions every 24 hrs. The effect on the tablet tensile strength of storage conditions alternating every 24 hrs between 33 and 75%, between 33 and 93%, and between 25 and 40°C is shown in Fig. 3, 4 and 5, respectively. Independent of the manufacturing technique daily changing RH between 75 and 33% only significantly affected the tensile strength of α-lactose monohydrate tablets containing PVP. The tensile strength obtained at 33% RH after prior storage at 75% RH was higher than without prior storage at 75% RH. The increase in tensile strength was completely reversible during the entire test period and was independent of the number of RH changes for tablets prepared by single-step granulation/tabletting.

a.



b.

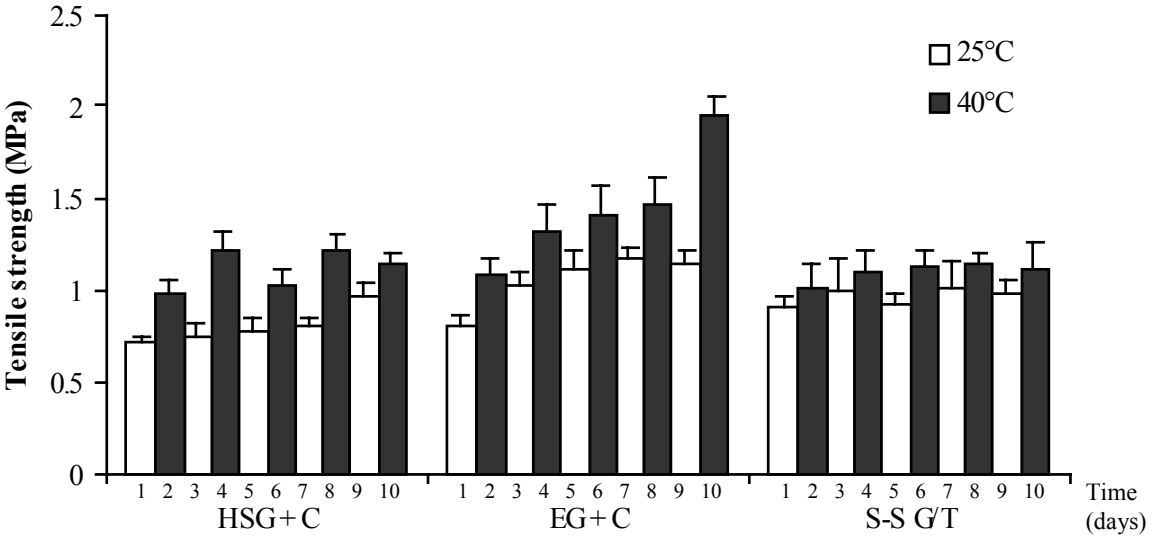


Figure 5: Tensile strength (mean ± sd, n=6) of α-lactose monohydrate tablets, prepared by high shear granulation + compression (HSG + C), extrusion/granulation + compression (EG + C), direct compression (DC) and single-step granulation/tabletting (S-S G/T). Tablets were stored (33% RH) for 10 days at 25 and 40°C, alternating the temperature every 24 hrs between both conditions. (a) tablets without binder, (b) tablets with 2.5% PVP.

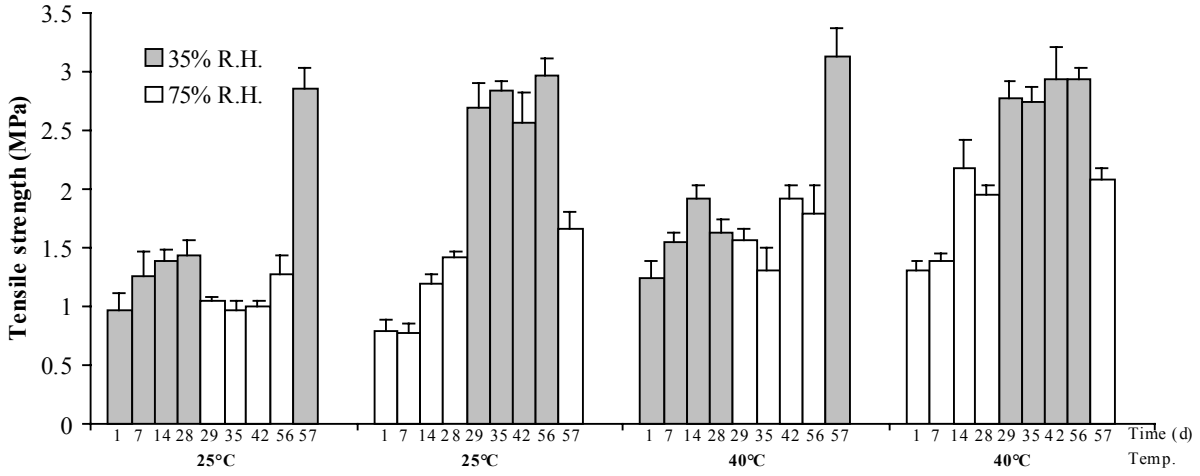


Figure 6: Tensile strength (mean ± sd, n=6) of α-lactose monohydrate tablets with 2.5% PVP, prepared by compression of granules prepared by extrusion/granulation. Tablets were stored (25 and 40°C) for 2 months at 33 and 75% RH, alternating the RH every month between both conditions.

However, tensile strength increased with increasing number of changes in case of the compressed tablets as during each storage period at high RH, additional contact points were formed by swelling and migration of the rubbery PVP between the lactose particles. In case of the tablets prepared by single-step granulation/tabletting, having a more porous structure, the increase in tensile strength was unlikely to be caused by the formation of additional contact points, but solely to the rubber-to-glass transition of PVP, which is a reversible phenomenon (Mc Phillips et al. 1999).

A significant increase in tensile strength was seen at 33% RH for tablets (with and without PVP) prepared by compression of granules made by extrusion when RH during storage alternated daily between 93 and 33% RH (Fig. 4). It was interesting to observe that for pure α-lactose monohydrate tablets the tensile strength at 93% RH gradually increased with the number of changes to a value similar as the one obtained at 33% RH. This clearly confirmed that hardening of α-lactose monohydrate tablets only occurred after initial storage above the critical RH at which sufficient moisture is absorbed to allow partial dissolution. In tablets containing PVP, significantly higher tensile strengths were recorded than those observed under any condition for tablets prepared by single-step granulation/tabletting. This could

again be explained by a combination of additional solid bridges formed by α-lactose monohydrate and the rubber-to-glass transition of PVP.

Changing the storage temperature revealed a significant increase in tensile strength at 40°C after prior storage at 25°C (Fig. 5). As for RH, these changes depended on the formulation as well as on the manufacturing technique. Tablets prepared by single-step granulation/tabletting were not affected by changing the temperature, whereas tablets prepared by compression of granules tended to get stronger on repeatedly transferring the tablets between both temperatures (especially when containing PVP). This effect is explained by the condensation of moisture, which occurs more easily in smaller pores resulting in the formation of solid bridges (Ahlneck and Alderborn, 1989a and b).

In addition to the effect of the number of changes, the effect of the initial storage period after which conditions were altered was also evaluated. Comparison of these tensile strength values with those obtained after daily changing, revealed that changing RH after one month from 75% to 33% RH resulted in higher tensile strength (2.69 MPa) than changing after one day (1.80 MPa), but the effect remained reversible. Studying the effect of changing RH after one year revealed that this did not cause an additional increase in tensile strength (2.50 MPa). These results indicated that although time and temperature enhance the formation of solid bridges, at a certain level not much more additional contact points can be formed that significantly contribute to tablet hardening.

11.6 Conclusion

From these results it was concluded that tablets produced by single-step granulation/tabletting, where bonding mainly occurred by solid bridges, were not affected by storage conditions that showed to induce hardening of compressed tablets (time, temperature and changing from high to low RH). However, due to their porous structure these tablets are more susceptible to tablet weakening by glass-to-rubber transition of the binder (PVP).

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General conclusion and recommendations

The increasing demand for granulation and the discovery of new drugs that are potent or expensive urge the development of new wet granulation techniques, which complies with the GMP requirements, operated in a continuous way and possibly conducted in a closed circuit with the possibility of automation. Although extrusion has been studied as a granulation technique research on this topic are sparse. Therefore this study was aim to develop continuous wet granulation processes based on cold extrusion technology.

Extrusion granulation using twin screw extruder was the first process studied. Evaluations conducted on extrusion granulation revealed a semi-continuous process resulting in better granule and tablet properties compared to the conventional high shear granulation. In order to have a continuous granulation process based on extrusion granulation, some modifications were carried out on the twin screw extruder. Modification of screw profile and removal of the extruder die block resulted in elimination of the wet sizing step as during extrusion granulation where a continuous production of granules was obtained. This process showed a high efficiency for continuous granulation of pharmaceutical formulations, even for formulations that were difficult to process using high shear granulation. This novel technique was called continuous twin screw granulation (CTSG).

Single-step granulation/tabletting was also developed in order to improve tablet properties and eliminate a compression step. This process resulted in tablets with higher quality than those produced by compression. The bonding mechanism involved during single-step granulation/tabletting is behind the improvement of the tablet properties. Study of the mechanism showed that tablets produced by single-step granulation/tabletting are bound by solid bridges with a high porosity, whereas compressed tablets were bound by intermolecular forces with a much lower porosity. In addition those tablets did not harden during storage at different conditions, but were more susceptible to the influence of storage conditions when containing PVP.

In general this study presented a promising techniques for continuous wet granulation, however further work is recommended. As further research work the following suggestions are formulated:

- To assess the possibility of using larger continuous twin screw granulators based on geometrical similarities with continuous twin screw granulator.

- The uniformity of active components within granules especially for low dosed and micronized drugs after twin screw granulation and single step granulation/tabletting processes.

- Optimization of the properties of tablets produced by single step granulation/tabletting in order to reduce weight variation and improve tablet appearance.

- Assess the possibility of continuous drying by optimization of the formulation variables and incorporation of a drying device that allow continuous drying in a short period of time.

- The study of the granulation mechanism during twin screw granulation.

- Assess the feasibility of controlling granule properties like porosity and particle size distribution by machine modification and optimization of processing parameters.

Summary

In the pharmaceutical industry wet granulation is considered the most important process in manufacturing of solid dosage forms. The majority of the granulation processes are batch processes, which often showed problems during product development and scaling up. The increase demand for granules and the development of new expensive and potent drugs urged further research for the development of a contained and integrated wet granulation process with the possibility of continuity and automation. In recent years few continuous wet granulation processes were established. Those processes are reviewed in Chapter 1. Extrusion granulation was among those techniques, and was not subjected to extensive research. Chapter 1 illustrates different types of extruders with a detailed description of the twin screw extruder.

This thesis aimed at evaluating the feasibility of using twin screw extrusion for wet granulation and to develop a continuous wet granulation process that fulfils the needs of the pharmaceutical industry. The objectives of this study are listed in Chapter 2.

Chapter 3 describes extrusion granulation as a semi-continuous wet granulation process. During this process the extrudates were produced and wet sized. The influence of processing parameters and formulation variables on the properties of α-lactose monohydrate 200M granules was evaluated. Tablets were produced from the 250-710 µm granule fraction and were evaluated. The properties of granules and tablets obtained by extrusion granulation were compared with those obtained after high shear granulation. Results showed that granules prepared by extrusion had a higher quality than those obtained by high shear granulation.

The extrusion granulation process was used for the granulation of different types of lactose and also for formulations containing paracetamol and cimetidine. Granules and tablets were evaluated and compared with those produced by high shear granulation. The different lactose grades had an important effect on the extrusion granulation process, but had only a minor influence on the granule and tablet properties obtained by extrusion granulation however, the lactose grades had a major influence on the granule properties obtained by high shear granulation.

Granules and tablets of paracetamol and cimetidine prepared by extrusion granulation exhibited higher qualities than those produced by high shear granulation. Chapter 4.

In Chapter 5 the modification of a twin screw extruder for continuous wet granulation was investigated. Modification of the extruder set-up as well as the screw design allowed the continuous wet granulation of α-lactose monohydrate 200M without the need of a wet sieving step. This new machine set-up was termed continuous twin screw granulation. The influence of processing parameters and formulation variables on the process performance and on the properties of granules and tablets was evaluated. Granules and tablets obtained showed good properties. Meanwhile no problems were observed during continuous twin screw granulation over a period of 8 h and the granule and tablet properties were reproducible throughout the process.

In Chapter 6 the efficiency and robustness of continuous twin screw granulation was assessed. The process was applied to different types of lactose, paracetamol and cimetidine. Granules produced were evaluated. Tablets were made from those granules and were also evaluated. The lactose grades had an important effect on the continuous twin screw granulation process but had only a minor influence on the granule and tablet properties obtained. Granulation of cimetidine and paracetamol exhibited a high yield and a low friability. Tablets made using those granules showed good properties. The results obtained indicated that continuous twin screw granulation is efficient wet granulation technique.

In Chapter 7 the feasibility of cold extrusion as a continuous granulation/tableting technique was investigated. α-Lactose monohydrate 200M extrudates were produced using twin-screw extrusion, cut manually into tablets and dried. The influence of formulation and process parameters on the process and on the tablet properties was evaluated. Formulation as well as process parameters affected the process feasibility, but had only a minor effect on the tablet properties. This technique allows single-step granulation/tableting of pure α-lactose monohydrate indicating that cold extrusion could be used as alternative tablet production technique for ingredients with poor compaction properties. All α-lactose monohydrate tablets without and with PVP produced at optimum conditions showed a high tensile strength and fast disintegration time. This high tensile strength and fast disintegration was attributed to the bonding mechanism. This bonding mechanism was evaluated in Chapter 8 where tablets containing α-lactose monohydrate, paracetamol, cimetidine and PVP were prepared

using single-step granulation/tabletting, high shear granulation/compression, extrusion granulation/compression and direct compression. The internal tablet structure was analysed by SEM and porosity measurements. The bonding mechanism was assessed by calculation of the interaction factor and determination of the electrical conductivity. Analysis of the internal tablet structure revealed that tablets prepared by single-step granulation/tabletting had a porous, sponge like structure, while the compressed tablets showed a dense structure. Tablets manufactured by single-step granulation/tabletting had a higher interaction factor and a significantly lower resistivity than compressed tablets, indicating that solid bridges were involved.

In Chapter 9 the influence of the lactose particle size, morphology and crystallinity on the single-step granulation/tabletting and on the quality of tablets obtained were investigated. Results showed that particle size and type of lactose affected the powder feeding, the process performance as well as the process capacity. Different grades of lactose yielded tablets with similar tensile strength, but significantly different disintegration time. Single-step granulation/tabletting always yielded tablets with a significantly higher tensile strength and similar or significantly lower disintegration time compared to high shear granulation and compression. The properties of α-lactose monohydrate tablets without and with PVP, did not change during one year of storage at 60% RH-25°C and at 75% RH-40°C.

In Chapter 10 Paracetamol tablets and cimetidine tablets were prepared by single-step granulation/tabletting and by compression after high shear granulation and were compared. Paracetamol tablets and cimetidine tablets obtained by single-step granulation/tabletting exhibited a significantly higher quality compared to those prepared by compression after high shear granulation. Single-step granulation/tabletting allowed to produce tablets containing up to 80% paracetamol or cimetidine with a dissolution profile complying with the USP requirements. Long term and accelerated stability studies of paracetamol tablets produced by single-step granulation/tabletting over a period of one year showed no significant influence on the tablet tensile strength, friability and dissolution. These results indicated that single-step granulation/tabletting could be an efficient technique for the production of highly dosed drugs such as paracetamol and cimetidine.

In Chapter 11 The influence of storage conditions (relative humidity, temperature and time) on the stability of α-lactose monohydrate 200M tablets prepared by single-step granulation/tabletting was studied and compared with tablets produced by compression. The study involved storage of tablets at different humidity and temperature for short and long term. In addition repeatedly changing the humidity and temperature storage conditions was also evaluated. Results obtained after storing tablets for short term showed that increasing relative humidity to 93% decreased tablet tensile strength. For tablets formulated with PVP the effect was more pronounced and observed at 75% RH. Changing of relative humidity conditions did not influence tablets without PVP produced by single-step granulation/tabletting, whereas it influenced tablets produced by compression after extrusion granulation. For tablets formulated with PVP changing of relative humidity conditions significantly influenced tablets produced by both techniques. This effect is dependent on the initial and final storage humidity conditions. In addition the number of humidity grade changes did not result in a progressive increase in the tensile strength for tablets produced by single-step granulation/tabletting, whereas tensile strength was increased with increasing the number of changes for tablets produced by compression. The temperature changes did not influence tablets produced by single-step granulation/tabletting, whereas repeatedly changing storage temperature resulted in stronger tablets for those prepared by compression after extrusion granulation. These results indicated that tablets produced by single-step granulation/tabletting do not harden during the storage conditions evaluated. However, these tablets were more susceptible to the weakening effect when containing PVP.

Samenvatting

Binnen de farmaceutische industrie wordt vochtige granulatie beschouwd als één van de belangrijkste technieken voor het produceren van vaste doseringsvormen. Terwijl de meeste granulatieprocessen batchgewijs verlopen is er – omwille van de schaalvergroting binnen de farmaceutische wereld, de toenemende vraag naar kwalitatieve granules en de synthese van nieuwe dure en sterk actieve geneesmiddelen – nood aan volledig geïntegreerde granulatieprocessen welke de mogelijkheid bieden op een continue manier te granuleren. Gedurende de laatste jaren werden reeds enkele continue vochtige granulatietechnieken ontwikkeld welke beschreven worden in Hoofdstuk 1. Eén van deze continue granulatiemethodes is extrusie/granulatie, een techniek waaraan tot op heden weinig aandacht is besteed binnen de farmaceutische industrie. Hoofdstuk 1 beschrijft eveneens de verschillende types extruders die beschikbaar zijn met specifieke aandacht voor de 'twin screw' extruders.

Het doel van deze thesis (Hoofdstuk 2) is het potentieel na te gaan van 'twin screw' extrusie als vochtige granulatietechniek en een continu vochtig granulatieproces te ontwikkelen dat volledig tegemoet komt aan de huidige noden van de farmaceutische industrie.

Hoofdstuk 3 beschrijft extrusie/granulatie als een semi-continue vochtige granulatietechniek, waarbij het noodzakelijk was het extrudaat vochtig te zeven alvorens granules werden bekomen. De invloed van proces- en formulatieparameters op de eigenschappen van α-lactose monohydraat 200M granules werd bepaald. Tabletten werden gecomprimeerd met behulp van de 250-710 µm granulaatfractie. De eigenschappen van granules en tabletten geproduceerd via extrusie/granulatie werden vergeleken met deze van materiaal geagglomereerd via 'high shear' granulatie. De resultaten toonden aan dat de granules geproduceerd via extrusie van een betere kwaliteit waren in vergelijking met deze bereid via 'high shear' granulatie.

Het extrusie/granulatie-proces werd eveneens aangewend voor het granuleren van verschillende types lactose en voor het agglomereren van formulaties op basis van paracetamol en cimetidine (Hoofdstuk 4). Opnieuw werd de kwaliteit van de granules en tabletten vergeleken met deze geproduceerd via 'high shear' granulatie. Het gebruik van verschillende lactoses had een belangrijke invloed tijdens het

extrusie/granulatie-proces, maar slechts een beperkte invloed op de granulaat- en tableteigenschappen. Daarentegen was de kwaliteit van granules geproduceerd via 'high shear' granulatie wel afhankelijk van het type lactose. Granulaten en tabletten geformuleerd met paracetamol of cimetidine en geproduceerd via extrusie/granulatie waren van betere kwaliteit in vergelijking met deze geproduceerd via 'high shear' granulatie.

Hoofdstuk 5 beschrijft hoe de 'twin extruder' werd gemodificeerd (extruder set-up en schroefdesign) zodat een volledig continu granulatieproces werd bekomen. Door middel van deze continue 'twin screw' granulatie-methode was het mogelijk α-lactose monohydraat 200M te agglomereren waarbij vochtig zeven niet noodzakelijk is. De invloed van proces- en formulatieparameters op het granulatieproces en op de granulaat- en tableteigenschappen werd bepaald. Zowel de granules als de tabletten hadden goede eigenschappen. Uit een granulatieexperiment uitgevoerd over een periode van 8 uren bleek dat de granulaat- en tableteigenschappen reproduceerbaar waren gedurende het volledige proces.

In Hoofdstuk 6 wordt de efficiëntie en de robuustheid van de continue 'twin screw' granulatie-methode nagegaan, dit door formulaties op basis van verschillende types lactose, paracetamol of cimetidine via deze techniek te agglomereren. Zowel de granulaatkwaliteit als de kwaliteit van tabletten geproduceerd met deze granules werd bepaald. Het type lactose had een belangrijke effect op het continue 'twin screw' granulatie-proces, maar het effect op de granulaat- en tablet-eigenschappen was beperkt. Granulatie van cimetidine en paracetamol werd gekenmerkt door een hoge opbrengst en een lage friabiliteit van de granules. Tabletten geproduceerd met deze granulaten waren van goede kwaliteit. Deze resultaten toonden aan dat de continue 'twin screw' granulatie-methode een efficiënte vochtige granulatie-techniek is.

In Hoofdstuk 7 werden de mogelijkheden geëvalueerd van extrusie als continue granulatie/tabletteer-techniek. Hierbij werden α-lactose monohydraat 200M extrudaten geproduceerd via 'twin-screw' extrusie, welke manueel tot tabletten werden gesneden en vervolgens gedroogd. De invloed van proces- en formulatieparameters op het extrusieproces en de tableteigenschappen werd bepaald. Hieruit bleek dat zowel de formulatie- als de procesparameters een invloed hadden op het extrusieproces, terwijl de tableteigenschappen slechts in beperkte mate werden beïnvloed. Aangezien deze 'single-step' techniek toelaat op een continue wijze tabletten te produceren kan deze techniek aangewend worden als alternatieve methode

voor het produceren van tabletten van materialen met beperkte compressie-eigenschappen. Zowel de α-lactose monohydraat tabletten geformuleerd zonder als met PVP hadden een hoge treksterkte en snelle desintegratietijd. Beide eigenschappen zijn het gevolg van het specifieke bindingsmechanisme tussen de individuele partikels in de tabletten geproduceerd via de extrusie/tabletteer-techniek. Het bindingsmechanisme wordt bestudeerd in Hoofdstuk 8 waarbij tabletten op basis van α-lactose monohydraat, paracetamol, cimetidine en PVP werden bereid zowel via 'single-step' granulatie/tabletteren, 'high shear' granulatie + compressie, extrusie/granulatie + compressie als directe compressie. De interne tabletstructuur werd geanalyseerd via scanning electronen microscopie en porositeitsmetingen. Het bindingsmechanisme werd bepaald door het berekenen van de interactiefactor en door het bepalen van de electrische geleidbaarheid. Analyse van de interne tabletstructuur toonde aan dat tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek een poreuze, sponsachtige structuur hadden, terwijl tabletten geproduceerd via klassieke compressie een dense structuur hadden. Tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek hadden een hoge interactiefactor en een significant lagere weerstand in vergelijking met gecomprimeerde tabletten, een indicatie dat vaste bruggen worden gevormd tussen de individuele deeltjes.

In Hoofdstuk 9 wordt de invloed van de deeltjesgrootte, morfologie en kristalliniteit van lactose op de 'single-step' granulatie/tabletteer-techniek en op de tabletkwaliteit bepaald. De resultaten toonden aan dat zowel het voedingssysteem van het poeder als het extrusieproces beïnvloed werden door de deeltjesgrootte en het type van lactose. De verschillende lactoses resulteerden in tabletten met een gelijkaardige treksterkte, maar een significant verschillende desintegratietijd. Via de 'single-step' granulatie/tabletteertechniek werden steeds tabletten geproduceerd met een significant hogere treksterkte en een gelijkaardige of significant lagere desintegratietijd in vergelijking met tabletten geproduceerd via 'high shear' granulatie en compressie. De eigenschappen van α-lactose monohydraat tabletten geformuleerd zonder of met PVP, wijzigden niet gedurende 1 jaar bewaring bij 60% RH/25°C en 75% RH/40°C.

In Hoofdstuk 10 werden paracetamol- en cimetidine-tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek en via compressie na 'high shear' granulatie. De 'single-step' granulatie/tabletteer-techniek resulteerde in tabletten met een significant betere kwaliteit en liet toe tabletten te produceren met 80% geneesmiddelbelading (zowel voor paracetamol als cimetidine) waarbij de dissolutie-

eigenschappen voldeden aan de eisen gesteld in de United States pharmacopoeia. Zowel een lange-termijn stabiliteitsstudie over een periode van 1 jaar als een versnelde stabiliteitsstudie toonden aan dat de eigenschappen van tabletten (treksterkte, friabiliteit, dissolutie) geproduceerd via de 'single-step' granulatie/tabletteer-techniek geen significante wijzigingen ondergingen in functie van de tijd. Deze resultaten toonden aan dat de 'single-step' granulatie/tabletteer-techniek een efficiënte methode is voor het produceren van tabletten beladen met hooggedoseerde geneesmiddelen (vb. paracetamol, cimetidine).

In Hoofdstuk 11 wordt de invloed bepaald van bewaring (relatieve vochtigheid, temperatuur en tijd) op de stabiliteit van α-lactose monohydrate 200M tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek in vergelijking met tabletten geproduceerd via compressie. Hierbij worden de tabletten zowel gedurende kortere periodes als gedurende langere periodes bewaard bij verschillende relatieve vochtigheden en temperaturen. De korte-termijn stabiliteitstudie toonde aan dat een relatieve vochtigheid van 93% de treksterkte van de tabletten deed dalen. Voor tabletten geformuleerd met PVP was deze daling meer uitgesproken en manifesteerde deze zich reeds vanaf 75% RV. Het variëren van de relatieve vochtigheid gedurende bewaren had geen invloed op tabletten (zonder PVP) geproduceerd via de 'single-step' granulatie/tabletteer-techniek, terwijl dit wel het geval was voor tabletten geproduceerd via compressie na extrusie/granulatie. In het geval van tabletten met PVP beïnvloedde een verandering van relatieve vochtigheid de kwaliteit van tabletten geproduceerd via beide technieken. In welke mate de tabletten beïnvloed werden was afhankelijk van zowel de condities aan het begin als op het einde van de bewaarperiode. Daarenboven resulteerde het aantal veranderingen van relatieve vochtigheid niet in een progressieve toename van de treksterkte van tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek, terwijl dit wel het geval was voor tabletten geproduceerd via extrusie/granulatie en compressie. De temperatuur had geen invloed op tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek, terwijl de treksterkte van tabletten geproduceerd via compressie na extrusie/granulatie toenam. Deze studie toonde aan dat tabletten geproduceerd via de 'single-step' granulatie/tabletteer-techniek niet uitharden onder invloed van de geteste bewaarcondities. Hierbij dient wel opgemerkt te worden dat de treksterkte van deze tabletten sneller daalde indien ze PVP bevatten.